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(54) Title: TREATMENT, PREVENTION AND AMELIORATION OF PULMONARY DISORDERS ASSOCIATED WITH CHEMOTHERAPY OR RADIOTHERAPY WITH ACTIVE VITAMIN D COMPOUNDS OR MIMICS THEREOF

(57) Abstract: The present invention relates to a method for preventing, treating or ameliorating pulmonary disorders in a patient receiving a chemotherapeutic or radiotherapeutic agent or treatment comprising administering to the patient a pharmaceutical composition comprising an effective amount of active vitamin D compound or a mimic thereof. According to the invention, the active vitamin D compound, or the mimic thereof, may be administered by HDPA so that high doses of the active vitamin D compound can be administered to an animal without inducing severe symptomatic hypercalcemia.

TREATMENT, PREVENTION AND AMELIORATION OF PULMONARY DISORDERS ASSOCIATED WITH CHEMOTHERAPY OR RADIOTHERAPY WITH ACTIVE VITAMIN D COMPOUNDS OR MIMICS THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention relates to a method for preventing, treating or ameliorating pulmonary disorders induced by or associated with chemotherapy or radiotherapy or treatment in an animal by administering to the animal active vitamin D compounds or a mimic thereof preferably by high dose pulse administration.

Related Art

[0002] Cancer chemotherapy often entails use of a combination of agents. U.S. Pat. No. 6,469,058. The choice of chemotherapy regimen suitable for a particular patient with a particular cancer depends on the cytotoxic agent and may vary from small doses taken one or more times a day to larger doses taken as infrequent as once a month. Regardless of their mechanism of actions, cytotoxic agents either kill cancer cells, or slowdown or stop cancer cell division. The success of the drug to treat cancer depends on its differential effect on cancer cells compared to normal cells.

[0003] In addition to treating or ameliorating cancer, chemotherapeutic agents may also cause unwanted side effects. Some of these side effects may be mild and treatable (such as dizziness, nausea, and some vomiting and/or diarrhea) while others are severe, life-threatening or even lethal. Among the more serious side effects are pulmonary toxicities that may lead to grades III-IV pneumonia, acute respiratory distress syndrome, or pulmonary fibrosis. Several cytotoxic drugs, including taxanes, bleomycin, methotrexate, busulfan, and the nitrosoureas may cause interstitial pneumonitis, alveolitis and

pulmonary fibrosis. Administration of multiple cytotoxic drugs and pre-existing lung disease may potentiate pulmonary toxicity. Gucalap, R. and Dutcher, J. "Oncologic emergencies," in Harrison's Principles of internal medicine, Vol. 1, Fauci, A. S. et al., eds., 14th ed., McGraw-Hill, New York, NY, pp.627-634 (1998).

[0004] Acute or subacute pneumonia generally affects the cells that line the alveoli, which are small sacs in the lungs that are responsible for exchanging oxygen from the air with carbon dioxide in the blood. Inflammation of these sensitive structures makes gas (oxygen and carbon dioxide) exchange less efficient, reducing the amount of oxygen that is absorbed from the air and delivered to the body. Various drugs used for the chemotherapy of cancer can damage lung tissues resulting in pneumonia. For example, 15% of patients suffering from head and neck cancer and treated with paclitaxel, a taxane similar to docetaxel (175 mg/m^2 over 3 hours on day 1), ifosfamide (1000 mg/m^2 over 2 hours on days 1-3), cisplatin (60 mg/m^2 IV day 1, repeated every 3-4 weeks), and mesna (600 mg/m^2 on days 1-3 in two divided doses, 400 mg/m^2 IV before ifosfamide and 200 mg/m^2 IV 4 hours after ifosfamide) required hospitalization due to pneumonia. Shin, D. M. *et al.*, *J. Clin. Oncol.* 16: 1325-30 (1998). Also, 7% of acute myelogenous patients treated with gemtuzumab (9 mg/m^2 IV over 2 hours, two doses with 14 days between the doses) suffered from grade III or IV pneumonia. Product package insert for Mylotarg™, Wyeth-Ayerst Pharmaceuticals, Inc. Moreover, 7% of patients with myeloid blast crisis treated with once a day oral dose of either 400 mg or 600 mg imatinib mesylate (Gleevec®) developed grade III or IV pneumonia. Product package insert for Gleevac®, Novartis Pharmaceutical Corporation. In two single-arm open-label studies of fludarabine phosphate (Fludara®) in patients with refractory chronic lymphocytic leukemia, 16% of patients receiving 22-40 mg/m^2 daily Fludara® injections for five days every 28 days and 22% of patients receiving 15-25 mg/m^2 daily Fludara® injection for five days every 28 days developed pneumonia. Product insert for Fludara®, Berlex Laboratories, Richmond, CA. Also, one of 44 cervical cancer patients treated with paclitaxel (135 mg/m^2 IV over 24 hours day 1), followed by cisplatin (75

mg/m^2 IV day 2, repeat every 21 days) developed grade III or IV pneumonia. Rose, P. G. *et al., J. Clin. Oncol.,* 17: 2678-80 (1999). Other cancer drugs that have been implicated to cause pneumonia with grade III or IV toxicity include alemtuzmab (Campath®). Indeed, the product package insert of Campath® indicates that prophylaxis directed against *Pneumocystis carinii* pneumonia used in connection with Campath® treatment decreases, but does not eliminate, the occurrence of this infection.

[0005] Another example of pulmonary toxicity induced by or associated with chemotherapy is pulmonary fibrosis. Pulmonary fibrosis is the development of fibrous scar tissue in the lungs. Lung tissue is normally very elastic and expands as one breathes in order to provide a larger space for air. As scar tissue builds up in the lung, in some cases as a result of acute inflammation, the air sacs of the lungs become gradually replaced by fibrotic tissue. When the scar forms, the tissue becomes thicker causing an irreversible loss of the tissue's ability to transfer oxygen into the bloodstream. Various drugs used for the chemotherapy of cancer cause pulmonary fibrosis. Bleomycin (BLM) is known to induce pulmonary complications. Indeed, 7 of 148 testicular cancer patients treated with bleomycin (30 units IV, weekly), etoposide (100 mg/m^2/d IV days 1-5) and cisplatin (20 mg/m^2/d IV days 1-5), repeat cycle every 3 weeks for four 3-week periods, experienced grade III-IV respiratory toxicity with 3 patient deaths due to pulmonary toxicity. Nichols, J. R., *et al. J. Clin. Oncol.* 16: 1287-93 (1998).

[0006] Acute Respiratory Distress Syndrome ("ARDS") is a life-threatening condition in which inflammation of the lungs and accumulation of fluid in the air sacs (alveoli) leads to low blood oxygen levels. ARDS can be caused by any major lung inflammation or injury. Some common causes include pneumonia, septic shock, trauma, aspiration of vomit, chemical inhalation and chemotherapy. When a patient is suffering from ARDS, blood concentration of oxygen can remain dangerously low in spite of supplemental oxygen delivered by a mechanical ventilator through an endotracheal tube and many will succumb to ARDS. Typically patients require care in an intensive care

unit. Symptoms usually develop within 24 to 48 hours of the original injury or illness.

[0007] Various drugs used for the chemotherapy of cancer damage the lung resulting in severe respiratory toxicities that can lead to ARDS. For example, 6 of 151 testicular cancer patients treated with cisplatin (20 mg/m^2/d IV, days 1-5), etoposide (75 mg/m^2/d IV, days 1-5), ifosfamide (1.2 g/m^2, days 1-5) and mesna (120 mg/m^2 IV before ifosfamide on day 1, followed by 1.2 g/m^2 on days 1-5), repeat cycle every 3 weeks for four 3-week periods, developed grade III-IV respiratory toxicity. Nichols, J. R., *et al.*, J. *Clin. Oncol.* 16: 1287-93 (1998). Also, 2 out of 40 patients with bladder cancer treated with gemcitabine 1200 mg/m^2 IV (administered weekly times three on a 4-week cycle) experienced grade III-IV respiratory toxicity. Stadler, W. M., *et al.*, *J. Clin. Oncol.* 15: 3394-98 (1997). Moreover, 18% of Non-Hodgkin's lymphoma patients treated with cyclophosphamide (600, 750 or 1000 mg/m^2 IV day 1) and fludarabine (20 mg/m^2/d IV over 30 minutes, days 1-5), repeat cycle for 3 or 4 weeks, developed grade III or IV pulmonary toxicity including a case of documented pneumocystis carinii pneumonia, leading to discontinuation of treatment for 11% of patients (3 of 27 patients) because of pulmonary toxicity. Hochster, H. S. *et al.*, *J. Clin. Oncol.* 18(5): 897-94 (2000). In addition, 7% of patients with newly diagnosed advanced Hodgkin's disease and treated with doxorubicin (25 mg/m^2 IV days 1, 15), bleomycin (10 mg/m^2 IV days 1, 15), vinblastine (6 mg/m^2 IV days 1, 15) and dacarbazine (375 mg/m^2 IV days 1, 15) developed grade III or IV pulmonary toxicity with a mortality rate of 3% due to pulmonary toxicity. Canellos, G. P. *et al.*, *N. Engl. J. Med.* 327(21): 1478-84 (1992). Twenty percent of acute promyelocytic leukemia patients treated with all-trans-retinoic acid developed severe (7%), life-threatening (11%) or lethal (2%) grade III or IV pulmonary toxicity. Tallman, M. S. *et al.*, *N. Eng. J. Med.*, 337(15): 1021-8 (1997).

[0008] Moreover, neutropenia is often associated with cancer chemotherapy. See, for example, Canellos, G. P. *et al.*, *N. Engl. J. Med.* 327(21): 1478-84 (1992); Stadler, W. M., *et al.*, *J. Clin. Oncol.* 15: 3394-98 (1997); Rose, P. G. *et al.*, *J. Clin. Oncol.*, 17: 2678-80 (1999). Neutropenia is an abnormally low

level of neutrophils in the blood and a large body of clinical data indicates that susceptibility to infectious diseases increase sharply when neurophil levels fall below 1000 cells/μL. Holland, S. M. and Gallin, J. I. "Disorders of Granulocytes and Monocytes," in Harrison's Principles of internal medicine, Vol. 1, Fauci, A. S. et al., eds., 14th ed., McGraw-Hill, New York, NY, pp.351-359 (1998). Moreover, control of endogenous microbial flora becomes impaired when the absolute neutrophil count falls below 500 cell/μL.

[0009] There are few compounds which provide direct protection from injuries caused by chemotherapy. One agent that has been reported to protect the kidney from injury caused by bolus infusions of cisplatin is S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR 2721). (See Glover, D. *et al., Pharmacol. Therap.* 39: 3-7(1988)). However, administered doses caused hypotension (7% of patients) and emesis (48% of patients). Moreover, U.S. Patent 5,605,931 teaches a method for protecting non-stomach tissue from injury resulting from administration of a chemotherapeutic agent by administering a therapeutic amount of an E-type prostaglandins. Other drugs that have been used to reduce chemotherapy-induced toxicities include Neupogen® and Ethyol®. Neupogen® is a recombinant human granulocyte colony-stimulating factor (see product label, Neupogen®, Amgen, Inc., Thousand Oaks, CA), which induces the bone marrow to accelerate the production of human polymorphonuclear leukocytes and to increase their microbial activity. Graybill, J. R. et al. *Antimicrobial Agents and Chemotherapy,* 42(10):2467-2473 (1998). Neupogen® decreases the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs that are associated with incidence of severe neutropenia. See product label for Neupogen®. Ethyol® is an organic thiophosphate cytoprotective agent known chemically as 2-[(3-aminopropyl)amino]ethanethiol dihydrogen phosphate and reduces the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small cell lung cancer. Product label for Ethyol®, marketed by Alza Pharmaceuticals, Palo Alto, CA and U.S. Bioscience, Inc., West Conshohocken, PA.

[0010] It would be desirable to provide effective protection against pulmonary toxicities induced by or associated with chemotherapy. It would be desirable that such protection is provided by a simple procedure which would assure compliance and not interfere with the beneficial therapeutic effects of the chemotherapy agents. The present invention provides for such a protection.

SUMMARY OF THE INVENTION

[0011] One aspect of the present invention is a method for preventing, treating or ameliorating pulmonary disorders in a patient receiving a chemotherapeutic or a radiotherapeutic agent or treatment comprising administering to the patient a pharmaceutical composition comprising an effective amount of an active vitamin D compound, or a mimic thereof.

[0012] In one embodiment of the invention, the active vitamin D compound, or a mimic thereof, is administered by high-dose pulse administration ("HDPA") so that high doses of the active vitamin D compound, or a mimic thereof, can be administered to an animal without inducing severe symptomatic hypercalcemia. In another embodiment of the invention, the active vitamin D compound, or a mimic thereof, is administered at a dose sufficient to obtain a peak plasma concentration of the active vitamin D compound of at least 0.5 nM.

[0013] In another embodiment, the active vitamin D compound, or a mimic thereof, is administered as a unit dosage form comprising about 10 μg to about 200 μg of calcitriol, about 50% MIGLYOL 812 and about 50% tocopherol PEG-1000 succinate (vitamin E TPGS). More preferably, the active vitamin D compound, or a mimic thereof, is administered as a unit dosage form comprising about 45 μg, about 90 μg, about 135 μg or about 180 μg. The active vitamin D compound or a mimic thereof may be administered orally, intravenously, parenterally, rectally, topically, nasally, sublingually, intramuscularly or transdermally. It is understood that the terms "about 50% MIGLYOL 812" and "about 50% tocopherol PEG-1000 succinate (vitamin E TPGS)" together encompass an amount less than 100% such that one or more

active ingredients or other additives may be present in the composition without the composition components totaling more than 100%.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The present invention provides a method for protecting pulmonary cells and tissues from injury produced by chemotherapy or radiotherapy. Specifically, it has been surprisingly discovered that late stage prostate cancer patients (i.e., patients with androgen independent prostate cancer) treated with Taxotere® and intermittent high doses of calcitriol (i.e., doses as high as 300 μg/day) experienced fewer pulmonary disorders, including acute respiratory distress syndrome, pneumonia and pulmonary fibrosis. Prevention of these side effects is beneficial in reducing the morbidity of cancer chemotherapy or radiotherapy and/or allowing for a higher and more curative dose regimen of chemotherapy or radiotherapy to be delivered to cancer patients without these severe side effects.

[0015] Accordingly, the present invention relates to a method for preventing, treating or ameliorating side effects induced by or associated with chemotherapy or radiotherapy. In particular, the method relates to amelioration, prevention or treatment of pulmonary disorders induced by or associated with the chemotherapy or radiotherapy of a variety of cancers including, but not limited to, brain cancer, breast cancer, gastrointestinal cancers comprising colon, colorectal, esophageal, gastric, hepatocellular, pancreatic and rectal cancers, genitourinary cancers comprising bladder, prostate, renal cell and testicular cancers, gynecologic cancers comprising cervical, endometrial, ovarian and uterine cancers, head and neck cancer, leukemias comprising acute lymphoblastic, acute myelogenous, acute promyelocytic, chronic lymphocytic, chronic myelogenous, and hairy cell leukemias, non-small-cell and small-cell lung cancers, Hodgkin's and non-Hodgkin's lymphomas, melanoma, multiple myeloma and sarcoma.

[0016] In one aspect of the invention, the active vitamin D compound has a reduced hypercalcemic effect, allowing higher doses of the compound to be

administered to an animal without inducing severe symptomatic hypercalcemia.

[0017] As used herein, the term "therapeutically effective amount" refers to that amount of the therapeutic agent sufficient to result in prevention of a pulmonary disorder, e.g., pneumonia, pulmonary fibrosis or acute respiratory distress syndrome, amelioration of one or more symptoms of a pulmonary disorder, or prevention of advancement of a pulmonary disorder. For example, with respect to the treatment of pneumonia, pulmonary fibrosis, acute respiratory distress syndrome, dyspnea or hypoxia, a therapeutically effective amount preferably refers to the amount of a therapeutic agent that reduces the extent of pneumonia, pulmonary fibrosis, acute respiratory distress syndrome, dyspnea or hypoxia by at least 10%, preferably at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100%. The extent of pneumonia, pulmonary fibrosis, acute respiratory distress syndrome, dyspnea or hypoxia can be determined by any method known in the art.

[0018] The terms "prevent, preventing, and prevention," as used herein, are intended to refer to a decrease in the occurrence of a pulmonary disorder. The prevention may be complete, *e.g.*, the total absence of a pulmonary disorder. The prevention may also be partial, such that pulmonary disorder is less than that which would have occurred without the present invention. For example, the extent of pulmonary disorder using the methods of the present invention may be at least 10%, preferably at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% less than the amount of pulmonary disorder that would have occurred without the present invention.

[0019] The term "cancer," as used herein, is intended to refer to any known cancer, and may include, but is not limited to the following: leukemias such as acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia leukemias, and myelodysplastic syndrome; chronic leukemias such as chronic myelocytic (granulocytic) leukemia, chronic lymphocytic

leukemia, and hairy cell leukemia; polycythemia vera; lymphomas such as Hodgkin's disease and non-Hodgkin's disease; multiple myelomas such as smoldering multiple myeloma, non-secretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma and extramedullary plasmacytoma; Waldenstrom's macroglobulinemia; monoclonal gammopathy of undetermined significance; benign monoclonal gammopathy; heavy chain disease; bone and connective tissue sarcomas such as bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; brain tumors such as glioma, astrocytoma, brain stem glioma, ependymoma, oligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; breast cancers such as adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mucinous breast cancer, tubular breast cancer, papillary breast cancer, Paget's disease of the breast, and inflammatory breast cancer; adrenal cancers such as pheochromocytoma and adrenocortical carcinoma; thyroid cancers such as papillary or follicular thyroid cancer, medullary thyroid cancer and anaplastic thyroid cancer; pancreatic cancers such as insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; pituitary cancers such as prolactin-secreting tumor and acromegaly; eye cancers such as ocular melanoma, iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; vaginal cancers such as squamous cell carcinoma, adenocarcinoma, and melanoma; vulvar cancers such as squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease of the genitals; cervical cancers such as squamous cell carcinoma and adenocarcinoma; uterine cancers such as endometrial carcinoma and uterine sarcoma; ovarian cancers such as ovarian epithelial carcinoma, ovarian epithelial borderline tumor, germ cell tumor, and stromal

tumor; esophageal cancers such as squamous cancer, adenocarcinoma, adenoid cyctic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; stomach cancers such as adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; colon cancers; rectal cancers; liver cancers such as hepatocellular carcinoma and hepatoblastoma, gallbladder cancers such as adenocarcinoma; cholangiocarcinomas such as papillary, nodular, and diffuse; lung cancers such as non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma and small-cell lung cancer; testicular cancers such as germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor), prostate cancers such as adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; penile cancers; oral cancers such as squamous cell carcinoma; basal cancers; salivary gland cancers such as adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; pharynx cancers such as squamous cell cancer and verrucous; skin cancer s such as basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, acral lentiginous melanoma; head and neck cancers; kidney cancers such as renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, transitional cell cancer (renal pelvis and/or ureter); Wilms' tumor; and bladder cancers such as transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma. In addition, cancers that can be treated by the methods and compositions of the present invention include myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangioendotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma and papillary adenocarcinoma. See Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia, PA and Murphy et al., 1997, Informed Decisions:

The Complete Book of Cancer Diagnosis, Treatment, and Recovery, Viking Penguin, New York, NY, for a review of such disorders.

[0020] As used herein, the term "pulmonary disorders induced by or associated with" refers to any pulmonary disorder that a patient develops during, or at the end of, chemotherapy or radiotherapy. This term is intended to include all pulmonary disorders a patient suffers during chemotherapy or radiotherapy, or just after it ended, regardless of whether a direct or indirect causal link between the chemotherapy or radiotherapy and the disorder can be demonstrated. In one embodiment, pulmonary disorders developed within five weeks after the end of chemotherapy or radiotherapy are included in "pulmonary disorders induced by or associated with" chemotherapy or radiotherapy. In another embodiment, pulmonary fibrosis that takes up to several months to develop after the end of chemotherapy or radiotherapy are included in "pulmonary disorders induced by or associated with" chemotherapy or radiotherapy.

[0021] The term, "pulmonary disorder" as used herein includes pulmonary inflammation, fibrosis, dyspnea and hypoxia. Pulmonary inflammation may lead to pneumonia or acute respiratory distress syndrome. Thus, preventing, treating or ameliorating a pulmonary disorder will prevent, treat or ameliorate pneumonia, acute respiratory distress syndrome, pulmonary fibrosis, dyspnea or hypoxia.

[0022] The terms "pulmonary fibrosis," "interstitial lung disease" and "interstitial pulmonary fibrosis" as used herein refer to any lung disease where the lung tissues are damaged and the tissues between air sacs are scarred. The terms "pulmonary fibrosis," "interstitial lung disease" and "interstitial pulmonary fibrosis" also describe any abnormal formation of fiber-like scar tissue in the lungs, regardless of the origin. The scar formation is often preceded by, or associated with, inflammation. As fibrosis progresses, lung tissues thicken and become stiff, making breathing difficult. It can also be fatal. Although there are many different causes of pulmonary fibrosis, they all

include some insult to the lungs triggering inflammation and subsequent fibrosis.

[0023] As used herein, the term "acute respiratory distress syndrome" (ARDS) refers to a sudden, life-threatening lung failure. ARDS is not a specific disease but a syndrome. Regardless of the underlying condition, a person suffering from ARDS is faced with complete or near complete loss of lung function. Common causes of ARDS include infections and injury that cause inflammation and accumulation of fluid (edema) in the alveoli. Once alveoli fill with fluid, they collapse and the patient becomes starved of oxygen. Because ARDS develops as a result of any disease that directly or indirectly injures the lungs, pulmonary disorders associated with chemotherapy or radiotherapy can also lead to ARDS. The mortality rate from ARDS ranges from 35–50%. ARDS, adult respiratory distress syndrome, severe respiratory failure, pulmonary infiltrates and severe acute respiratory syndrome (SARS) are all synonyms and may be used interchangeably.

[0024] The term "dyspnea" as used herein refers to chemotherapy or radiotherapy-induced shortness of breath and the abnormally uncomfortable awareness of breathing associated with it.

[0025] The term "hypoxia" as used herein refers to respiratory hypoxia induced by chemotherapy or radiotherapy. Hypoxia is often caused by ventilation-perfusion mismatch (which results from perfusion of poorly ventilated alveoli), hypoventilation or shunting of blood from right to left by perfusion of nonventilated portions of the lung. Braunwald, E. "Hypoxia, Polycythemia, and Cyanosis" in Harrison's Principles of internal medicine, Vol. 1, Fauci, A. S. et al., eds., 14th ed., McGraw-Hill, New York, NY, pp. 205-210 (1998).

[0026] Chemotherapeutic agents useful in the invention include actinomycin D, irinotecan, vincristine, vinblastine, methotrexate, azathioprine, fluorouracil, doxorubicin, mitomycin, docetaxel, paclitaxel, cyclophosphamide, capecitabine, epirubicin, cisplatin, gemcitabine, mitoxantrone, leucovorin, vinorelbine, trastuzumab, etoposode, carboplatin, estramustine, prednisone, interferon alpha-2a, interleukin-2, bleomycin, ifosfamide, mesna, altretamine,

topotecan, cytarabine, methylprednisolone, dexamethasone, daunorubicin, intrathecal methotrexate, mercaptopurine, thioguanine, fludarabine, gemtuzumab, idarubicin, mitoxantrone, tretinoin, alemtuzumab, chlorambucil, cladribine, interferon α_{2b}, hydroxyurea, imatinib, epirubicin, dacarbazine, procarbazine, mechlorethamine, rituximab, denileukin diftitox, trimethoprim/sulfamethoxazole, allopurinol, carmustine, tamoxifen, filgrastim, temozolomide, melphalan, vinorelbine, SN-38, azacitidine (5-azacytidine, 5AzaC), thalidomide and mitomycin.

[0027] Therapeutic agents useful as adjunctive therapy according to the invention include, but are not limited to, small molecules, synthetic drugs, peptides, polypeptides, proteins, nucleic acids (*e.g.*, DNA and RNA polynucleotides including, but not limited to, antisense nucleotide sequences, triple helices, and nucleotide sequences encoding biologically active proteins, polypeptides, or peptides), antibodies, synthetic or natural inorganic molecules, mimetic agents, and synthetic or natural organic molecules. Any agent which is known to be useful, or which has been used or is currently being used for the prevention, treatment, or amelioration of pulmonary disorders can be used in combination with an active vitamin D compound, or a mimic thereof, in accordance with the invention described herein.

[0028] The term "radiotherapeutic agent," as used herein, is intended to refer to any radiotherapeutic agent known to one of skill in the art to be effective to treat or ameliorate cancer, without limitation. For instance, the radiotherapeutic agent can be an agent such as those administered in brachytherapy or radionuclide therapy. Such methods can optionally further comprise the administration of one or more additional cancer therapies, such as, but not limited to, chemotherapies, surgery, and/or another radiotherapy.

[0029] In certain embodiments involving radiotherapeutic agents or treatments, the present invention relates to a method for preventing, treating or ameliorating pulmonary disorders induced by or associated with radiotherapy comprising the administration of an active vitamin D compound, or a mimic thereof, in combination with a treatment comprising a therapeutically effective dose of brachytherapy. The brachytherapy can be administered according to

any schedule, dose, or method known to one of skill in the art to be effective in the treatment or amelioration of cancer, without limitation. In general, brachytherapy comprises insertion of radioactive sources into the body of a subject to be treated for cancer, preferably inside the tumor itself, such that the tumor is maximally exposed to the radioactive source, while preferably minimizing the exposure of healthy tissue.

[0030] In certain embodiments, the brachytherapy can be intracavitary brachytherapy. In other embodiments, the brachytherapy can be interstitial brachytherapy. Whether the brachytherapy is intracavitary brachytherapy or interstitial brachytherapy, the brachytherapy can be administered at a high dose rate, a continuous low dose rate, or a pulsed dose rate. For example, and not by way of limitation, a high dose rate brachytherapy regimen can be a dose of 60 Gy administered in ten fractions over six days, while a continuous low dose rate brachytherapy regimen can be a total dose of about 65 Gy, administered continuously at about 40 to 50 cGy per hour. Other examples of high, continuous low, and pulsed dose rate brachytherapy are well known in the art. See, e.g., Mazeron *et al.*, *Sem. Rad. Onc.* 12:95-108 (2002).

[0031] Representative radioisotopes that can be administered in any of the above-described brachytherapies include, but are not limited to, phosphorus 32, cobalt 60, palladium 103, ruthenium 106, iodine 125, cesium 137, iridium 192, xenon 133, radium 226, californium 252, or gold 198. Other radioisotopes may be selected for administration in brachytherapy according to the desirable physical properties of such a radioisotope. One of skill in the art will readily recognize that many properties will affect a radioisotope's suitability for use in brachytherapy, including, but not limited to, the radioisotope's half-life, the degree to which emitted radiation penetrates surrounding tissue, the energy of emitted radiation, the ease or difficulty of adequately shielding the radioisotope, the availability of the radioisotope, and the ease or difficulty of altering the shape of the radioisotope prior to administration.

[0032] Additional methods of administering and apparatuses and compositions useful for brachytherapy are described in U.S. Patent Nos. 6,319,189,

6,179,766, 6,168,777, 6,149,889, and 5,611,767, each of which is incorporated herein by reference in its entirety.

[0033] In certain embodiments, the present invention relates to a method for preventing, treating or ameliorating pulmonary disorders induced by or associated with radiotherapy comprising the administration of an active vitamin D compound, or a mimic thereof, in combination with a treatment comprising a therapeutically effective dose of a radionuclide. The radionuclide therapy can be administered according to any schedule, dose, or method known to one of skill in the art to be effective in the treatment or amelioration of cancer, without limitation. In general, radionuclide therapy comprises systemic administration of a radioisotope that preferentially accumulates in or binds to the surface of cancerous cells. The preferential accumulation of the radionuclide can be mediated by a number of mechanisms, including, but not limited to, incorporation of the radionuclide into rapidly proliferating cells, specific accumulation of the radionuclide by the cancerous tissue without special targeting (*e.g.*, iodine 131 accumulation in thyroid cancer), or conjugation of the radionuclide to a biomolecule specific for a neoplasm.

[0034] Representative radioisotopes that can be administered in radionuclide therapy include, but are not limited to, phosphorus 32, yttrium 90, dysprosium 165, indium 111, strontium 89, samarium 153, rhenium 186, iodine 131, iodine 125, lutetium 177, and bismuth 213. While all of these radioisotopes may be linked to a biomolecule providing specificity of targeting, iodine 131, indium 111, phosphorus 32, samarium 153, and rhenium 186 may be administered systemically without such conjugation. One of skill in the art may select a specific biomolecule for use in targeting a particular neoplasm for radionuclide therapy based upon the cell-surface molecules present on that neoplasm. For example, hepatomas may be specifically targeted by an antibody specific for ferritin, which is frequently over-expressed in such tumors. Examples of antibody-targeted radioisotopes for the treatment of cancer include ZEVALIN (ibritumomab tiuxetan) and BEXXAR

(tositumomab), both of which comprise an antibody specific for the B cell antigen CD20 and are used for the treatment of non-Hodgkin lymphoma.

[0035] Other examples of biomolecules providing specificity for particular cell are reviewed in an article by Thomas, *Cancer Biother. Radiopharm. 17*:71-82 (2002), which is incorporated herein by reference in its entirety. Furthermore, methods of administering and compositions useful for radionuclide therapy may be found in U.S. Patent Nos. 6,426,400, 6,358,194, 5,766,571, and 5,563,250, each of which is incorporated herein by reference in its entirety.

[0036] The term "radiotherapeutic treatment," as used herein, is intended to refer to any radiotherapeutic treatment known to one of skill in the art to be effective to treat or ameliorate cancer, without limitation. For instance, the radiotherapeutic treatment can be external-beam radiation therapy, thermotherapy, radiosurgery, charged-particle radiotherapy, neutron radiotherapy, or photodynamic therapy. Such methods can optionally further comprise the administration of one or more additional cancer therapies, such as, but not limited to, chemotherapies, surgery, and/or another radiotherapy.

[0037] In certain embodiments involving radiotherapeutic agents or treatments, the present invention relates to a method for preventing, treating or ameliorating pulmonary disorders induced by or associated with radiotherapy comprising the administration of an active vitamin D compound, or a mimic thereof, in combination with a treatment comprising a therapeutically effective dose of external-beam radiation therapy. The external-beam radiation therapy can be administered according to any schedule, dose, or method known to one of skill in the art to be effective in the treatment or amelioration of cancer, without limitation. In general, external-beam radiation therapy comprises irradiating a defined volume within a subject with a high energy beam, thereby causing cell death within that volume. The irradiated volume preferably contains the entire cancer to be treated, and preferably contains as little healthy tissue as possible.

[0038] In certain embodiments, the external-beam radiation therapy can be three-dimensional conformal radiotherapy. In other embodiments, the

external-beam radiation therapy can be continuous hyperfractionated radiotherapy. In still other embodiments, the external-beam radiation therapy can be intensity-modulated radiotherapy. In yet other embodiments, the external-beam radiation therapy can be helical tomotherapy. In still other embodiments, the external-beam radiation therapy can be three dimensional conformal radiotherapy with dose escalation. In yet other embodiments, the external-beam radiation therapy can be stereotactic radiotherapy, including, but not limited to, single fraction stereotactic radiotherapy, fractionated stereotactic radiotherapy, and fractionated stereotactically guided conformal radiotherapy.

[0039] The external-beam radiation therapy can be generated or manipulated by any means known to one of skill in the art. For example, the photon beam used in external-beam radiation therapy can be shaped by a multileaf collimator. Other examples of suitable devices for generating a photon beam for use in external-beam radiation therapy include a gamma knife and a linac-based stereotactic apparatus. In certain embodiments, administration of the external-beam radiation therapy is controlled by a computer according to a three-dimensional model of the patient in the treatment position. Such a model can be generated, for example, by computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computer tomography (SPECT), and positron emission tomography (PET). Use of such visualization methods can advantageously minimize the volume of healthy tissue treated, thereby allowing higher total doses of radiation to be administered to the patient.

[0040] In addition, healthy tissues can optionally be protected from the effects of the external-beam radiation therapy by placing blocking devices such as, *e.g.*, lead shields, in locations where such protection is needed. Alternatively or additionally, metal reflecting shields can optionally be located to reflect the photon beam in order to concentrate the radiation on the cancerous tissue to be treated and protect healthy tissue. Placement of either shield is well within the knowledge of one of skill in the art.

[0041] Methods of administering and apparatuses and compositions useful for external-beam radiation therapy can be found in U.S. Patent Nos. 6,449,336, 6,398,710, 6,393,096, 6,335,961, 6,307,914, 6,256,591, 6,245,005, 6,038,283, 6,001,054, 5,802,136, 5,596,619, and 5,528,652, each of which is incorporated herein by reference in its entirety.

[0042] In certain embodiments involving radiotherapeutic agents or treatments, the present invention relates to a method for preventing, treating or ameliorating pulmonary disorders induced by or associated with radiotherapy comprising the administration of an active vitamin D compound, or a mimic thereof, in combination with a treatment comprising a therapeutically effective dose of thermotherapy. The thermotherapy can be administered according to any schedule, dose, or method known to one of skill in the art to be effective in the treatment or amelioration of cancer, without limitation. In certain embodiments, the thermotherapy can be cryoablation therapy. In other embodiments, the thermotherapy can be hyperthermic therapy. In still other embodiments, the thermotherapy can be a therapy that elevates the temperature of the tumor higher than in hyperthermic therapy.

[0043] Cryoablation therapy involves freezing of a neoplastic mass, leading to deposition of intra- and extra-cellular ice crystals; disruption of cellular membranes, proteins, and organelles; and induction of a hyperosmotic environment, thereby causing cell death. Cryoablation can be performed in one, two, or more freeze-thaw cycles, and further the periods of freezing and thawing can be adjusted for maximum tumor cell death by one of skill in the art. One exemplary device that can be used in cryoablation is a cryoprobe incorporating vacuum-insulated liquid nitrogen. See, *e.g.*, Murphy *et al.*, *Sem. Urol. Oncol. 19*:133-140 (2001). However, any device that can achieve a local temperature of about -180°C to about -195°C can be used in cryoablation therapy. Methods for and apparatuses useful in cryoablation therapy are described in U.S. Patent Nos. 6,383,181, 6,383,180, 5,993,444, 5,654,279, 5,437,673, and 5,147,355, each of which is incorporated herein by reference in its entirety.

[0044] Hyperthermic therapy typically involves elevating the temperature of a neoplastic mass to a range from about 42°C to about 44°C. The temperature of the cancer may be further elevated above this range; however, such temperatures can increase injury to surrounding healthy tissue while not causing increased cell death within the tumor to be treated. The tumor may be heated in hyperthermic therapy by any means known to one of skill in the art without limitation. For example, and not by way of limitation, the tumor may be heated by microwaves, high intensity focused ultrasound, ferromagnetic thermoseeds, localized current fields, infrared radiation, wet or dry radiofrequency ablation, laser photocoagulation, laser interstitial thermic therapy, and electrocautery. Microwaves and radiowaves can be generated by waveguide applicators, horn, spiral, current sheet, and compact applicators.

[0045] Other methods of and apparatuses and compositions for raising the temperature of a tumor are reviewed in an article by Wust *et al.*, Lancet Oncol. 3:487-97 (2002), and described in U.S. Patent Nos. 6,470,217, 6,379,347, 6,165,440, 6,163,726, 6,099,554, 6,009,351, 5,776,175, 5,707,401, 5,658,234, 5,620,479, 5,549,639, and 5,523,058, each of which is incorporated herein by reference in its entirety.

[0046] In certain embodiments involving radiotherapeutic agents or treatments, the present invention relates to a method for preventing, treating or ameliorating pulmonary disorders induced by or associated with radiotherapy comprising the administration of an active vitamin D compound, or a mimic thereof, in combination with a treatment comprising a therapeutically effective dose of radiosurgery. The radiosurgery can be administered according to any schedule, dose, or method known to one of skill in the art to be effective in the treatment or amelioration of cancer, without limitation. In general, radiosurgery comprises exposing a defined volume within a subject to a manually directed radioactive source, thereby causing cell death within that volume. The irradiated volume preferably contains the entire cancer to be treated, and preferably contains as little healthy tissue as possible. Typically, the tissue to be treated is first exposed using conventional surgical techniques, then the radioactive source is manually directed to that area by a surgeon.

Alternatively, the radioactive source can be placed near the tissue to be irradiated using, for example, a laparoscope. Methods and apparatuses useful for radiosurgery are further described in Valentini *et al.*, Eur. J. Surg. Oncol. 28:180-185 (2002) and in U.S. Patent Nos. 6,421,416, 6,248,056, and 5,547,454, each of which is incorporated herein by reference in its entirety.

[0047] In certain embodiments involving radiotherapeutic agents or treatments, the present invention relates to a method for preventing, treating or ameliorating pulmonary disorders induced by or associated with radiotherapy comprising the administration of an active vitamin D compound, or a mimic thereof, in combination with a treatment comprising a therapeutically effective dose of charged-particle radiotherapy. The charged-particle radiotherapy can be administered according to any schedule, dose, or method known to one of skill in the art to be effective in the treatment or amelioration of cancer, without limitation. In certain embodiments, the charged-particle radiotherapy can be proton beam radiotherapy. In other embodiments, the charged-particle radiotherapy can be helium ion radiotherapy. In general, charged-particle radiotherapy comprises irradiating a defined volume within a subject with a charged-particle beam, thereby causing cellular death within that volume. The irradiated volume preferably contains the entire cancer to be treated, and preferably contains as little healthy tissue as possible. A method for administering charged-particle radiotherapy is described in U.S. Patent No. 5,668,371, which is incorporated herein by reference in its entirety.

[0048] In certain embodiments involving radiotherapeutic agents or treatments, the present invention relates to a method for preventing, treating or ameliorating pulmonary disorders induced by or associated with radiotherapy comprising the administration of an active vitamin D compound, or a mimic thereof, in combination with a treatment comprising a therapeutically effective dose of neutron radiotherapy. The neutron radiotherapy can be administered according to any schedule, dose, or method known to one of skill in the art to be effective in the treatment or amelioration of cancer, without limitation.

[0049] In certain embodiments, the neutron radiotherapy can be a neutron capture therapy. In such embodiments, a compound that emits radiation when

bombarded with neutrons and preferentially accumulates in a neoplastic mass is administered to a subject. Subsequently, the tumor is irradiated with a low energy neutron beam, activating the compound and causing it to emit decay products that kill the cancerous cells. Such compounds are typically boron containing compounds, but any compound that has a significantly larger neutron capture cross-section than common body constituents can be used. The neutrons administered in such therapies are typically relatively low energy neutrons having energies at or below about 0.5 eV. The compound to be activated can be caused to preferentially accumulate in the target tissue according to any of the methods useful for targeting of radionuclides, as described below, or in the methods described in Laramore, *Semin. Oncol.* *24*:672-685 (1997) and in U.S. Patents Nos. 6,400,796, 5,877,165, 5,872,107, and 5,653,957, each of which is incorporated herein by reference in its entirety.

[0050] In other embodiments, the neutron radiotherapy can be a fast neutron radiotherapy. In general, fast neutron radiotherapy comprises irradiating a defined volume within a subject with a neutron beam, thereby causing cellular death within that volume. The irradiated volume preferably contains the entire cancer to be treated, and preferably contains as little healthy tissue as possible. Generally, high energy neutrons are administered in such therapies, with energies in the range of about 10 to about 100 million eV. Optionally, fast neutron radiotherapy can be combined with charged-particle radiotherapy in the administration of mixed proton-neutron radiotherapy.

[0051] In certain embodiments involving radiotherapeutic agents or treatments, the present invention relates to a method for preventing, treating or ameliorating pulmonary disorders induced by or associated with radiotherapy comprising the administration of an active vitamin D compound, or a mimic thereof, in combination with a treatment comprising a therapeutically effective dose of photodynamic therapy. The photodynamic therapy can be administered according to any schedule, dose, or method known to one of skill in the art to be effective in the treatment or amelioration of cancer, without limitation. In general, photodynamic therapy comprises administering a

photosensitizing agent that preferentially accumulates in a neoplastic mass and sensitizes the neoplasm to light, then exposing the tumor to light of an appropriate wavelength. Upon such exposure, the photosensitizing agent catalyzes the production of a cytotoxic agent, such as, *e.g.*, singlet oxygen, which kills the cancerous cells.

[0052] Representative photosensitizing agents that may be used in photodynamic therapy include, but are not limited to, porphyrins such as porfimer sodium, 5-aminolaevulanic acid and verteporfin; chlorins such as temoporfin; texaphyrins such as lutetium texephyrin; purpurins such as tin etiopurpurin; phthalocyanines; and titanium dioxide. The wavelength of light used to activate the photosensitizing agent can be selected according to several factors, including the depth of the tumor beneath the skin and the absorption spectrum of the photosensitizing agent administered. The period of light exposure may also vary according to the efficiency of the absorption of light by the photosensitizing agent and the efficiency of the transfer of energy to the cytotoxic agent. Such determinations are well within the ordinary skill of one in the art.

[0053] Methods of administering and apparatuses and compositions useful for photodynamic therapy are disclosed in Hopper, *Lancet Oncol. 1*:212-219 (2000) and U.S. Patent Nos. 6,283,957, 6,071,908, 6,011,563, 5,855,595, 5,716,595, and 5,707,401, each of which is incorporated herein by reference in its entirety.

[0054] While not intending to be bound by any particular theory of operation, it is believed that active vitamin D compounds, or a mimic thereof, can enhance the sensitivity of cancerous cells to radiotherapy, and this enhanced sensitivity is due to changes in cell mechanisms regulating apoptosis and/or the cell cycle. In addition to preventing, treating or ameliorating pulmonary disorders induced by or associated with radiotherapy, administration of an active vitamin D compound, or a mimic thereof, may also enhance and expand the applicability of radiotherapy in the treatment or amelioration of cancer, that would otherwise not respond to current radiotherapy. Examples of hyperproliferative disorders that ordinarily would not respond well to

radiotherapy include, but are not limited to, oral melanoma, hemangiopericytomas, fibrosarcomas, and osteosarcomas. Further, sensitizing cells to treatment can allow use of a lower dose of radiotherapy, which reduces the side effects associated with the radiotherapy.

[0055] Radiotherapy can be administered to destroy tumor cells before or after surgery, before or after chemotherapy, and sometimes during chemotherapy. Radiotherapy may also be administered for palliative reasons to relieve symptoms of cancer, for example, to lessen pain. Total body radiotherapy can be administered to patients who are undergoing a bone marrow transplant, which is a procedure often performed with subjects having leukemia. In the case of a bone marrow transplant, a large single dose, or six to eight smaller doses of radiation, is administered to the whole body to destroy bone marrow cells in preparation for the transplant. Among the types of tumors that can be treated using radiotherapy are localized tumors that cannot be excised completely and metastases and tumors whose complete excision would cause unacceptable functional or cosmetic defects or be associated with unacceptable surgical risks.

[0056] It will be appreciated that both the particular radiation dose to be utilized in treating cancer and the method of administration will depend on a variety of factors. Thus, the dosages of radiation that can be used according to the methods of the present invention are determined by the particular requirements of each situation. The dosage will depend on such factors as the size of the tumor, the location of the tumor, the age and sex of the patient, the frequency of the dosage, the presence of other tumors, possible metastases and the like. Those skilled in the art of radiotherapy can readily ascertain the dosage and the method of administration for any particular tumor by reference to Hall, E. J., Radiobiology for the Radiobiologist, 5th edition, Lippincott Williams & Wilkins Publishers, Philadelphia, PA, 2000; Gunderson, L. L. and Tepper J. E., eds., Clinical Radiation Oncology, Churchill Livingstone, London, England, 2000; and Grosch, D. S., Biological Effects of Radiation, 2nd edition, Academic Press, San Francisco, CA, 1980, each of which is incorporated herein by reference.

[0057] Antibiotics useful for amelioration or treatment of pulmonary disorders include aminoglycosides, beta-lactams, glycopeptide antibiotics, macrolides, oxazolidinones, polymyxins, quinolones (fluoroquinolones), streptogramins, sulfonamides and tetracyclines. Aminoglycosides include amikacin, dibekacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, sisomycin, streptomycin and tobramycin. Beta-lactams include carbapenems such as ertapenem, imipenem and meropenem; cephalosporins such as cephalexin, cefuroxime, cefadroxil and penicillins. Penicillins include benzathine penicillin, benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V), procaine penicillin, methicillin, dicloxacillin, flucloxacillin, amoxicillin, ampicillin, piperacillin, ticarcillin, azlocillin and carbenicillin. Glycopeptide antibiotics include vancomycin, teicoplanin, ramoplanin and decaplanin. Macrolides suitable as antibiotics include erythromycin, azithromycin, clarithromycin, roxithromycin and ketolides. Oxazolidinones suitable as antibiotics include linezolid and quinupristin/dalfopristin. Polymyxins suitable as an antibiotic include polymyxin B and colistin. Quinolones (fluoroquinolones) suitable as an antibiotic include ciprofloxacin, enoxacin, grepafloxacin, levofloxacin, lomefloxacin, norfloxacin, sparfloxacin, ofloxacin, trovafloxacin and nalidixic acid. Tetracyclines suitable as an antibiotic include doxycycline, oxytetracycline and chlortetracycline.

[0058] Other therapeutic agents useful in the methods and compositions of the invention include vasodilators (*e.g.*, nitrates, calcium channel blockers), anticoagulants (*e.g.*, heparin), anti-platelet agents (*e.g.*, aspirin, blockers of IIb/IIIa receptors, clopidogrel), anti-thrombins (*e.g.*, hirudin, iloprost), immunosuppressants (*e.g.*, sirolimus, tranilast, dexamethasone, tacrolimus, everolimus, A24), collagen synthetase inhibitors (*e.g.*, halofuginone, propyl hydroxylase, C-proteinase inhibitor, metalloproteinase inhibitor), anti-inflammatories (*e.g.*, corticosteroids such as alclometasone, amcinonide, betamethasone, beclomethasone, budesonide, cortisone, clobetasol, clocortolone, desonide, dexamethasone, desoximetasone, diflorasone, flunisolide, fluticasone, fluocinonide, flurandrenolide, halcinonide,

hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisone, prednisolone and triamcinolone; non-steroidal anti-inflammatory drugs), 17β-estradiol, angiotensin converting enzyme inhibitors, colchicine, fibroblast growth factor antagonists, histamine antagonists, lovastatin, nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, thioprotease inhibitors, platelet-derived growth factor antagonists, nitric oxide, and angiopeptin. In one embodiment, the therapeutic agent is a taxane, *e.g.*, paclitaxel, docetaxel or abraxane.

[0059] Anti-inflammatory drugs suitable for ameliorating inflammations associated with pulmonary disorders include salicylates (such as aspirin, choline magnessium trisalicylate, methyl salicylate, salsalte and diflunisal), acetic acids (such as indomethacin, sulindac, tolmetin, aceclofenac and diclofenac), 2-arylpropionic acids or profens (such as ibuprofen, ketoprofen, naproxen, fenoprofen, flurbiprofen and oxaprozin), N-arylanthranilic acids or fenamic acids (such as mefenamic acid, flufenamic acid, and meclofenamate), enolic acids or oxicams (such as piroxicam and meloxicam), cox inhibitors (such as celecoxib, rofecoxib (withdrawn from market), valdecoxib, parecoxib and etoricoxib), sulphonanilides such as nimesulide; naphthylalkanones (such as nabumetone), pyranocarboxylic acids (such as etodolac) and pyrroles (such as ketorolac).

[0060] As used herein, the term "immunomodulatory agent" and variations thereof including, but not limited to, immunomodulatory agents, immunomodulants, immunomodulators or immunomodulatory drugs, refer to an agent that modulates a host's immune system. In particular, an immunomodulatory agent is an agent that alters the ability of a subject's immune system to respond to one or more foreign antigens. In a specific embodiment, an immunomodulatory agent is an agent that shifts one aspect of a subject's immune response, *e.g.*, the agent shifts the immune response from a Th1 to a Th2 response. In certain embodiments, an immunomodulatory agent is an agent that inhibits or reduces a subject's immune system (*i.e.*, an immunosuppressant agent). In certain other embodiments, an

immunomodulatory agent is an agent that activates or increases a subject's immune system (*i.e.*, an immunostimulatory agent).

[0061] Immunomodulatory agents useful for the present invention include, but are not limited to, small molecules, peptides, polypeptides, proteins, nucleic acids (*e.g.*, DNA and RNA nucleotides including, but not limited to, antisense nucleotide sequences, triple helices and nucleotide sequences encoding biologically active proteins, polypeptides or peptides), antibodies, synthetic or natural inorganic molecules, mimetic agents, and synthetic or natural organic molecules. A particularly useful immunomodulatory agent useful for the present invention is thalidomide.

[0062] Immunosuppressant agents are useful to counteract autoimmune diseases, such as rheumatoid arthritis or Crohn's disease, and to prevent the immune system from attacking healthy parts of the body. In some embodiments, immunosuppressive agents useful for the present invention include glucocorticoid receptor agonists (e.g., cortisone, dexamethasone, hydrocortisone, betamethasone), calcineurin inhibitors (e.g., macrolides such as tacrolimus and pimecrolimus), immunophilins (e.g., cyclosporin A) and mTOR inhibitors (e.g., sirolimus, marketed as RAPAMUNE® by Wyeth). In other embodiments, immunomodulatory agents useful for the present invention further include antiproliferative agents (e.g., methotrexate, leflunomide, cisplatin, ifosfamide, paclitaxol, taxanes, topoisomerase I inhibitors (*e.g.*, CPT-11, topotecan, 9-AC, and GG-211), gemcitabine, vinorelbine, oxaliplatin, 5-fluorouracil (5-FU), leucovorin, vinorelbine, temodal, taxol, cytochalasin B, gramicidin D, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, melphalan, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin homologs, and cytoxan.

[0063] Immunostimulant agents are useful to increase the efficiency of the immune system and treat immunodeficiency disorders. Immunostimulant agents useful for the present invention include interferon and Zidovudine (AZT).

[0064] The term "an active vitamin D compound, or a mimic thereof, in combination with one or more therapeutic agents," as used herein, is intended to refer to the combined administration of an active vitamin D compound, or a mimic thereof, and one or more therapeutic agents or treatments, wherein the active vitamin D compound, or the mimic thereof, can be administered prior to, concurrently with, or after the administration of the therapeutic agents or treatments. The active vitamin D compound, or the mimic thereof, can be administered up to two weeks or more prior to or after the therapeutic agents or treatments and still be considered to be a combination treatment.

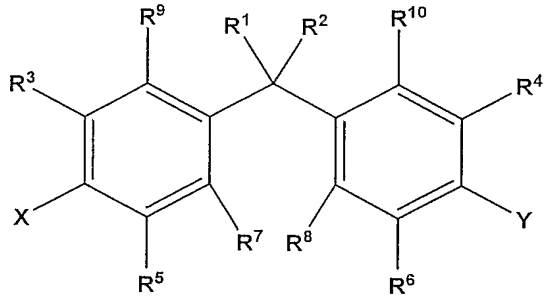
[0065] The term "active vitamin D compound," as used herein, is intended to refer to a vitamin D compound that is or becomes biologically active when administered to a subject or contacted with cells. The biological activity of a vitamin D compound can be assessed by assays well known to one of skill in the art such as, *e.g.*, immunoassays that measure the expression of a gene regulated by vitamin D. Vitamin D compounds exist in several forms with different levels of activity in the body. For example, a vitamin D compound may be partially activated by first undergoing hydroxylation in the liver at the carbon-25 position and then may be fully activated in the kidney by further hydroxylation at the carbon-1 position. The prototypical active vitamin D compound is 1α,25-hydroxyvitamin D_3, also known as calcitriol. The active vitamin D compound of the present invention may also be a partially hydroxylated vitamin D such as 1α-hydroxyvitamin D_3, also known as 1α-calcidol, and 25-hydroxyvitamin D_3, also known as calcifediol. A large number of other active vitamin D compounds are known and can be used in the practice of the invention. The active vitamin D compounds of the present invention include, but are not limited to, the analogs, homologs and derivatives of vitamin D compounds described in the following patents: U.S. Patent Nos. 4,391,802 (1α-hydroxyvitamin D derivatives); 4,717,721 (1α-hydroxy derivatives with a 17 side chain greater in length than the cholesterol or ergosterol side chains); 4,851,401 (cyclopentano-vitamin D analogs); 4,866,048 and 5,145,846 (vitamin D_3 analogues with alkynyl,

alkenyl, and alkanyl side chains); 5,120,722 (trihydroxycalciferol); 5,547,947 (fluoro-cholecalciferol compounds); 5,446,035 (methyl substituted vitamin D); 5,411,949 (23-oxa-derivatives); 5,237,110 (19-nor-vitamin D compounds; 4,857,518 (hydroxylated 24-homo-vitamin D derivatives). Particular examples include ROCALTROL (Roche Laboratories); CALCIJEX injectable calcitriol; investigational drugs from Leo Pharmaceuticals including EB 1089 (24a,26a,27a-trihomo-22,24-diene-1αa,25-$(OH)_2$-D_3, KH 1060 (20-epi-22-oxa-24a,26a,27a-trihomo-1α,25-$(OH)_2$-D_3), MC 1288 (1,25-$(OH)_2$-20-epi-D_3) and MC 903 (calcipotriol, 1α24s-$(OH)_2$-22-ene-26,27-dehydro-D_3); Roche Pharmaceutical drugs that include 1,25-$(OH)_2$-16-ene-D_3, 1,25-$(OH)_2$-16-ene-23-yne-D_3, and 25-$(OH)_2$-16-ene-23-yne-D_3; Chugai Pharmaceuticals 22-oxacalcitriol (22-oxa-1α,25-$(OH)_2$-D_3; 1α-(OH)-D_5 from the University of Illinois; and drugs from the Institute of Medical Chemistry-Schering AG that include ZK 161422 (20-methyl-1,25-$(OH)_2$-D_3) and ZK 157202 (20-methyl-23-ene-1,25-$(OH)_2$-D_3); 1α-(OH)-D_2; 1α-(OH)-D_3 and 1α-(OH)-D_4. Additional examples include 1α,25-$(OH)_2$-26,27-d_6-D_3; 1α,25-$(OH)_2$-22-ene-D_3; 1α ,25-$(OH)_2$-D_3; 1α,25-$(OH)_2$-D_2; 1α,25-$(OH)_2$-D_4; 1α,24,25-$(OH)_3$-D_3; 1α,24,25-$(OH)_3$-D_2; 1α,24,25-$(OH)_3$-D_4; 1α-(OH)-25-FD_3; 1α-(OH)-25-FD_4; 1α-(OH)-25-FD_2; 1α,24-$(OH)_2$-D_4; 1α,24-$(OH)_2$-D_3; 1α,24-$(OH)_2$-D_2; 1α,24-$(OH)_2$-25-FD_4; 1α,24-$(OH)_2$-25-FD_3; 1α,24-$(OH)_2$-25-FD_2; 1α,25-$(OH)_2$-26,27-F_6-22-ene-D_3; 1α,25-$(OH)_2$-26,27-F_6-D_3; 1α,25S-$(OH)_2$-26-F_3-D_3; 1α,25-$(OH)_2$-24-F_2-D_3; 1α,25S,26-$(OH)_2$-22-ene-D_3; 1α,25R,26-$(OH)_2$-22-ene-D_3; 1α,25-$(OH)_2$-D_2; 1α,25-$(OH)_2$-24-epi-D_3; 1α,25-$(OH)_2$-23-yne-D_3; 1α,25-$(OH)_2$-24R-F-D_3; 1α,25S,26-$(OH)_2$-D_3; 1α,24R-$(OH)_2$-25F-D_3; 1α,25-$(OH)_2$-26,27-F_6-23-yne-D_3; 1α,25R-$(OH)_2$-26-F_3-D_3; 1α,25,28-$(OH)_3$-D_2; 1α,25-$(OH)_2$-16-ene-23-yne-D_3; 1α,24R,25-$(OH)_3$-D_3; 1α,25-$(OH)_2$-26,27-F_6-23-ene-D_3; 1α,25R-$(OH)_2$-22-ene-26-F_3-D_3; 1α,25S-$(OH)_2$-22-ene-26-F_3-D_3; 1α,25R-$(OH)_2$-D_3-26,26,26-d_3; 1α,25S-$(OH)_2$-D_3-26,26,26-d_3; and 1α,25R-$(OH)_2$-22-ene-D_3-26,26,26-d_3. Additional examples can be found in U.S. Patent No. 6,521,608. *See also, e.g.*, U.S. Patent Nos. 6,503,893, 6,482,812, 6,441,207, 6,410,523, 6,399,797, 6,392,071, 6,376,480, 6,372,926, 6,372,731, 6,359,152, 6,329,357, 6,326,503, 6,310,226, 6,288,249, 6,281,249, 6,277,837, 6,218,430,

6,207,656, 6,197,982, 6,127,559, 6,103,709, 6,080,878, 6,075,015, 6,072,062, 6,043,385, 6,017,908, 6,017,907, 6,013,814, 5,994,332, 5,976,784, 5,972,917, 5,945,410, 5,939,406, 5,936,105, 5,932,565, 5,929,056, 5,919,986, 5,905,074, 5,883,271, 5,880,113, 5,877,168, 5,872,140, 5,847,173, 5,843,927, 5,840,938, 5,830,885, 5,824,811, 5,811,562, 5,786,347, 5,767,111, 5,756,733, 5,716,945, 5,710,142, 5,700,791, 5,665,716, 5,663,157, 5,637,742, 5,612,325, 5,589,471, 5,585,368, 5,583,125, 5,565,589, 5,565,442, 5,554,599, 5,545,633, 5,532,228, 5,508,392, 5,508,274, 5,478,955, 5,457,217, 5,447,924, 5,446,034; 5,414,098, 5,403,940, 5,384,313, 5,374,629, 5,373,004, 5,371,249, 5,430,196, 5,260,290, 5,393,749, 5,395,830, 5,250,523, 5,247,104, 5,397,775, 5,194,431, 5,281,731, 5,254,538, 5,232,836, 5,185,150, 5,321,018, 5,086,191, 5,036,061, 5,030,772, 5,246,925, 4,973,584, 5,354,744, 4,927,815, 4,804,502, 4,857,518, 4,851,401, 4,851,400, 4,847,012, 4,755,329, 4,940,700, 4,619,920, 4,594,192, 4,588,716, 4,564,474, 4,552,698, 4,588,528, 4,719,204, 4,719,205, 4,689,180, 4,505,906, 4,769,181, 4,502,991, 4,481,198, 4,448,726, 4,448,721, 4,428,946, 4,411,833, 4,367,177, 4,336,193, 4,360,472, 4,360,471, 4,307,231, 4,307,025, 4,358,406, 4,305,880, 4,279,826, and 4,248,791.

[0066] The term "mimic" as used herein is intended to refer to non-secosteroidal vitamin D mimic compounds. In general, these non-secosteroidal vitamin D mimics are compounds that do not structurally fall within the class of compounds generally known as vitamin D compounds but which modulate the activity of vitamin D nuclear receptors. Examples of such vitamin D mimics include bis-aryl derivatives disclosed by U.S. Patent 6,218,430 and WO publication 2005/037755. Additional examples of non-secosteroidal vitamin D mimic compounds suitable for the present invention can be found in U.S. patents 6,831,106; 6,706,725; 6,689,922; 6,548,715; 6,288,249; 6,184,422, 6,017,907, 6,858,595 and 6,358,939.

[0067] In one aspect the invention is drawn to methods employing non-secosteroidal vitamin D mimic compounds having Formula I:

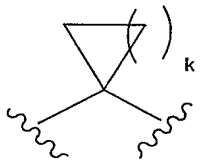


(I)

wherein:

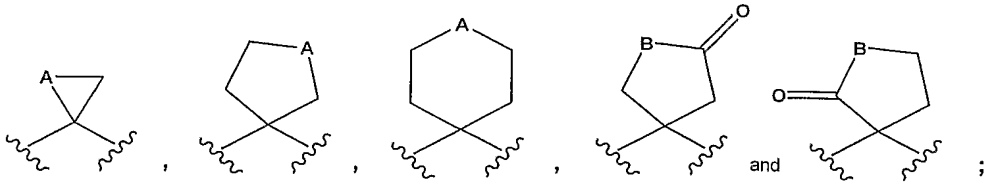
R^1 and R^2 are each independently halo, haloalkyl, pseudohalo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl or optionally substituted heteroaryl; or

R^1 and R^2, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl consisting of:



wherein k is an integer from 1 to 6; or

R^1 and R^2, together with the carbon atom to which they are attached, form an optionally substituted heterocyclyl selected from a group consisting of:



;

wherein A is -O-, $-NR^x-$, -S-, -S(O)- or $-S(O)_2-$ wherein R^x is hydrogen, alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-R^{14}-C(J)R^{15}$, $-R^{14}-C(J)OR^{15}$, $-R^{14}-C(J)R^{16}OR^{15}$, $-R^{14}-C(J)SR^{16}$, $-R^{14}-C(J)N(R^{18})R^{19}$, $-R^{14}-C(J)N(R^{17})N(R^{18})R^{19}$, $-R^{14}-C(J)N(R^{17})S(O)_pR^{20}$, $-R^{14}-S(O)_pN(R^{18})R^{19}$, or

$-R^{14}-S(O)_pR^{20}$; and wherein B is -O-, -S- or $-NR^y$ where R^y is hydrogen, alkyl, haloalkyl, aryl or heteroaryl; and wherein each p is independently 0 to 2;

R^3 and R^4 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, pseudohalo, nitro, cyano, azido, $-R^{14}-OR^{15}$, $-R^{14}-N(R^{18})R^{19}$, $-R^{14}-SR^{15}$, $-R^{14}-OC(J)R^{15}$, $-R^{14}-NR^{17}C(J)R^{15}$, $-R^{14}-OC(J)N(R^{18})R^{19}$, $-R^{14}-NR^{17}C(J)N(R^{18})R^{19}$, $-R^{14}-NR^{17}C(J)OR^{15}$, $-R^{14}-C(J)R^{15}$, $-R^{14}-C(J)OR^{15}$, $-R^{14}-C(J)SR^{15}$, $-R^{14}-C(J)N(R^{18})R^{19}$, or $-R^{14}-C(J)N(R^{17})N(R^{18})R^{19}$;

R^5, R^6, R^7, R^8, R^9, R^{10} are each independently hydrogen, halo, hydroxy, amino, pseudohalo, cyano, nitro, alkyl, haloalkyl, alkoxy or haloalkoxy;

X is R^{25};

Y is independently R^{30}, $-OR^{31}$, $-SR^{32}$ or $-N(R^{33})(R^{34})$;

R^{25} and R^{30} are each independently selected from (i) or (ii) as follows:

(i) optionally substituted alkyl that may be substituted with one to ten substituents each independently selected from a group consisting of halo, pseudohalo, nitro, cyano, thioxo, azido, amidino, guanidino, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{15}$, $-OR^{16}OR^{15}$, $-N(R^{18})R^{19}$, $-N(R^{17})N(R^{18})R^{19}$, $-SR^{15}$, $-SR^{16}SR^{15}$, $-N(R^{17})N(R^{17})S(O)_pR^{20}$, $-OC(J)R^{15}$, $-NR^{17}C(J)R^{15}$, $-OC(J)N(R^{18})R^{19}$, $-NR^{17}C(J)N(R^{18})R^{19}$, $-NR^{17}C(J)OR^{15}$, $-OC(J)OR^{15}$, $-P(R^{21})_2$, $-P(O)(R^{21})_2$, $-OP(O)(R^{21})_2$, $-C(J)R^{15}$, $-C(J)OR^{15}$, $-C(J)SR^{16}$, $-C(J)(R^{18})R^{19}$, $-C(J)N(R^{17})N(R^{18})R^{19}$, $-C(J)N(R^{17})N(R^{17})S(O)_pR^{20}$, $-C(R^{17})=NOR^{15}$, $-C(R^{17})=NR^{17}$, $-C(R^{17})=NN(R^{18})R^{19}$ and $-C(=NR^{17})N(R^{18})R^{19}$; or

(ii) optionally substituted alkenyl or optionally substituted alkynyl, either of which may be substituted with one to ten substituents each independently selected from a group consisting of oxo, thioxo, halo, pseudohalo, nitro, cyano, azido, amidino, guanidino, $-OR^{15}$, $-OR^{16}OR^{15}$, $-N(R^{18})R^{19}$, $-N(R^{17})N(R^{18})R^{19}$, $-SR^{15}$, $-SR^{16}SR^{15}$, $-S(O)_pR^{20}$, $-N(R^{17})S(O)_pR^{20}$, $-N(R^{17})N(R^{17})S(O)_pR^{20}$, $-OC(J)R^{15}$, $-NR^{17}C(J)R^{15}$, $-OC(J)N(R^{18})R^{19}$,

$-NR^{17}C(J)N(R^{18})R^{19}$, $-NR^{17}C(J)OR^{15}$, $-OC(J)OR^{15}$, $-P(R^{21})_2$, $-P(O)(R^{21})_2$, $-OP(O)(R^{21})_2$, $-C(J)R^{15}$, $-C(J)OR^{15}$, $-C(J)SR^{16}$, $-C(J)N(R^{18})R^{19}$, $-C(J)N(R^{17})N(R^{18})R^{19}$, $-C(J)N(R^{17})S(O)_pR^{20}$, $-C(J)N(R^{17})N(R^{17})S(O)_pR^{20}$, $-C(R^{17})=NOR^{15}$, $-C(R^{17})=NR^{17}$, $-C(R^{17})=NN(R^{18})R^{19}$, $-C(=NR^{17})N(R^{18})R^{19}$, alkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl;

R^{31}, R^{32}, R^{33}, and R^{34} are each independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl or optionally substituted cycloalkyl; all of which may be optionally substituted with one to ten substituents each independently selected from a group consisting of oxo, halo, pseudohalo, nitro cyano, azido, amidino, guanidino $-OR^{15}$, $-OR^{16}OR^{15}$, $-N(R^{18})R^{19}$, $-N(R^{17})N(R^{18})R^{19}$, $-SR^{15}$, $-SR^{16}SR^{15}$, $-S(O)_pR^{20}$, $-N(R^{17})S(O)_pR^{20}$, $-N(R^{17})N(R^{17})S(O)_pR^{20}$, $-OC(J)R^{15}$, $-NR^{17}C(J)R^{15}$, $-OC(J)N(R^{18})R^{19}$, $-NR^{17}C(J)N(R^{18})R^{19}$, $-NR^{17}C(J)OR^{15}$, $-OC(J)OR^{15}$, $-P(R^{21})_2$, $-P(O)(R^{21})_2$, $-OP(O)(R^{21})_2$, $-C(J)R^{15}$, $-C(J)OR^{15}$, $-C(J)SR^{16}$, $-C(J)N(R^{18})R^{19}$, $-C(J)N(R^{17})N(R^{18})R^{19}$, $-C(J)N(R^{17})S(O)_pR^{20}$, $-C(J)N(R^{17})N(R^{17})S(O)_pR^{20}$, $-C(R^{17})=NOR^{15}$, $-C(R^{17})=NR^{17}$, $-C(R^{17})=NN(R^{18})R^{19}$, $-C(=NR^{17})N(R^{18})R^{19}$, alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, and R^{34} can additionally be hydrogen;

where each R^{14} is independently a direct bond or alkylene;

where each R^{15} and R^{17} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl or optionally substituted heteroaryl, all of which, when substituted, are substituted with one to five substituents each independently selected from halo, cyano, hydroxy and amino;

where each R^{16} and R^{20} is independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl or optionally substituted heteroaryl, all of which, when substituted, are substituted with one to five substituents each independently selected from halo, hydroxy, alkoxy and amino; and

where each R^{18} and R^{19} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl or optionally substituted heteroaryl, all of which, when substituted, are substituted with one to five substituents each independently selected from halo, hydroxy, alkoxy and amino;

or where R^{18} and R^{19}, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl;

each R^{21} is independently alkyl, $-OR^{22}$ or $-N(R^{23})R^{24}$;

R^{22} is hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or aralkyl;

R^{23} and R^{24} are each independently hydrogen, alkyl, haloalkyl, alkenyl, alkynyl or cycloalkyl;

or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl;

each J is independently O or S;

as a single isomer, a mixture of isomers, or as a racemic mixture of isomers; as a solvate or polymorph; or as a prodrug or metabolite; or as a pharmaceutically acceptable salt thereof.

[0068] In one embodiment, R^1 and R^2 may form a substituted cyclohexyl, said cyclohexyl, when substituted at the 4-position relative to the gem-diaryl substituents, may be substituted with a substituent selected from the group consisting of halo, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl and optionally substituted heteroaryl.

[0069] In another embodiment, R^{25} and R^{30} are not $-CH_2COOH$; $-CH_2$-5-tetrazolyl; $-CH_2COOMe$; $-CH_2COOEt$; $-CH_2NH(CH_2COOH)$; $-CH_2N(C(O)Me)(CH_2COOH)$; $-CH_2$-N-pyrrolidin-2-one; $-CH_2$-(1-methylpyrrolidin-2-one-3-yl); $-CH_2C(O)NH_2$; $-CH_2C(O)NMe_2$; $-CH_2C(O)NHMe$; $-CH_2C(O)$-N-pyrrolidone; $-CH(OH)COOH$; $-CH(OH)C(O)NH_2$; $-CH(OH)C(O)NHMe$; $-CH(OH)C(O)NMe_2$; $-CH(OH)C(O)NEt_2$; $-CH_2CH_2COOH$; $-CH_2CH_2COOMe$; $-CH_2CH_2COOEt$;

$-CH_2CH_2C(O)NH_2$; $-CH_2CH_2C(O)NHMe$; $-CH_2CH_2C(O)NMe_2$; or $-CH_2CH_2$-5-tetrazolyl.

[0070] In another aspect the invention is drawn to methods employing the following non-secosteroidal vitamin D mimic compounds:

3-(2-methyl-4-{2,2,2-trifluoro-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-1-phenyl-ethyl}-phenoxy)-propane-1,2-diol;

3-(4-{4-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-piperidin-4-yl}-2-methyl-phenoxy)-propane-1,2-diol;

3-(4-{4-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-piperidin-4-yl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

1-{4-[4-(2(S),3-dihydroxy-propoxy)-3-methyl-phenyl]-4-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-piperidin-1-yl}-ethanone;

1-(4-{1-acetyl-4-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-piperidin-4-yl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-one;

3-(4-{1-ethyl-1-[4-(3-hydroxy-3-methylbutyl)-3-methylphenyl]-propyl}-2-methylphenoxy)-propane-1,2(S)-diol;

3-(4-{1-ethyl-1-[4-(3-ethyl-3-hydroxypentyl)-3-methylphenyl]-propyl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

3-(4-{1-ethyl-1-[4-(3-hydroxy-5-methylhexyl)-3-methylphenyl]-propyl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

3-(4-{1-ethyl-1-[4-(3-hydroxy-4-methylpentyl)-3-methylphenyl]-propyl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

3-(2-ethyl-4-{1-ethyl-1-[4-(3-hydroxy-4,4-dimethylpentyl)-3-methylphenyl]-propyl}-phenoxy)-propane-1,2(S)-diol;

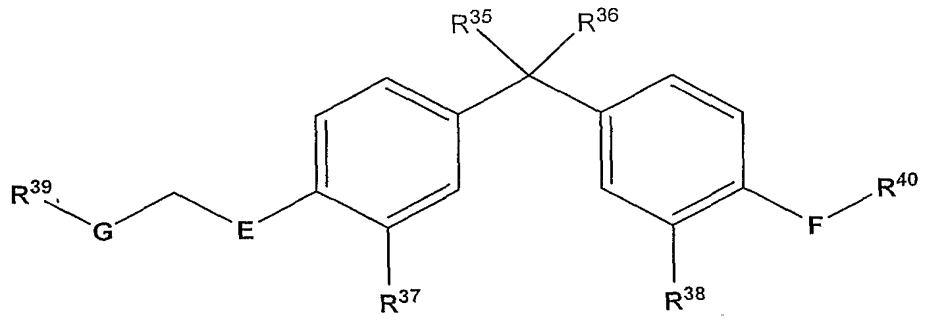
3-(4-{1-ethyl-1-[4-(3-hydroxy-4,4-dimethylpentyl)-3-methylphenyl]-propyl}-2-methyl-phenoxy)-propane-1,2(S)-diol;

3-[4-(1-ethyl-1-{4-[3(S)-hydroxy-4,4-dimethylpentyl]-3-methylphenyl}-propyl)-2-methyl-phenoxy]-propane-1,2(S)-diol;

3-[4-(1-ethyl-1-{4-[3(R)-hydroxy-4,4-dimethylpentyl]-3-methylphenyl}-propyl)-2-methyl-phenoxy]-propane-1,2(S)-diol and

3-(4-{1-ethyl-1-[4-(3-hydroxy-4,4-dimethylpentyl)-phenyl]-propyl}-2-methylphenoxy)-propane-1,2(S)-diol.

[0071] In another aspect the invention is drawn to methods employing non-secosteroidal vitamin D mimic compounds having Formula II:



II

wherein:

E and F are each independently selected from the group consisting of O, S, and NR^{41};

G is selected from the group consisting of C=O, $CH(OR^{42})$, and $CH(NR^{43}R^{44})$;

R^{35} and R^{36} are independently selected from the group consisting of alkyl groups, optionally fluorinated; or together R^{35} and R^{36} form a cycloalkylidene having 3 to 8 carbon atoms, optionally fluorinated;

R^{37} and R^{38} are independently selected from the group consisting of halogen; lower n-alkyl, optionally fluorinated; and lower alkoxy, optionally fluorinated;

R^{39} is selected from the group consisting of H; optionally substituted alkyl groups; optionally substituted alkenyl groups; optionally substituted alkynyl groups; optionally substituted aryl groups; OR^{45}; $NR^{46}R^{47}$; or together with R^{42}, R^{43}, or R^{44} forms a 3- to 12-membered cyclic group wherein said cyclic group is selected from the group consisting of amidines, amines, ethers, lactams, lactones, ketals, hemiketals, aminals, hemiaminals, carbonates, carbamates, ureas, and combinations thereof;

R^{40} is selected from the group consisting of H and alkyl groups, optionally substituted;

R^{41} is selected from the group consisting of H and alkyl groups, optionally substituted;

R^{42} is selected from the group consisting of H, optionally substituted alkyl groups, optionally substituted alkenyl groups, optionally substituted alkynyl groups, optionally substituted aryl group, and optionally substituted acyl groups;

R^{43} and R^{44} are independently selected from the group consisting of H, optionally substituted alkyl groups, optionally substituted alkenyl groups, optionally substituted alkynyl groups, optionally substituted aryl groups, and optionally substituted acyl groups;

R^{45} is selected from the group consisting of H, optionally substituted alkyl groups, optionally substituted alkenyl groups, optionally substituted alkynyl groups, optionally substituted aryl groups, and optionally substituted acyl groups; and

R^{46} and R^{47} are independently selected from the group consisting of H, optionally substituted alkyl groups, optionally substituted alkenyl groups, optionally substituted alkynyl groups, optionally substituted aryl groups, and optionally substituted acyl groups and pharmaceutically acceptable salts thereof.

[0072] In a first embodiment, when K and L are both O, M is C=O, and R^{45} is selected from the group consisting of OH and C_1 -C_4 alkoxy, then R^{46} is not carboxymethyl and alkyl esters thereof. In a second embodiment, when K and L are both O, and M is selected from the group consisting of $CH(OR^{48})$ and $CH(NR^{49}\ R^{50})$, then R^{45} is not H or primary alkyl. In a third embodiment, when K and L are both O, and M is $CH(OR^{48})$, then R^{46} and R^{48} do not both comprise aziridines. In a fourth embodiment, when K and L are both O, and M is $CH(OR^{48})$, then R^{45}, R^{46}, and R^{48} do not simultaneously comprise alkenyl ethers. In a fifth embodiment, when K and L are both O, and M is $CH(OR^{48})$, then R^{45} and R^{46} do not both comprise glycidyl ethers.

[0073] The term "high dose pulse administration" (HDPA) as used herein is intended to refer to a regimen of administration of an active vitamin D compound, or a mimic thereof, to an animal which achieves the desired result of preventing, treating or ameliorating a pulmonary disorder in the animal

without inducing severe symptomatic hypercalcaemia, e.g., a dose of at least 0.5 μg no more than once every three days.

[0074] The term "hypercalcemia" as used herein refers to a medical condition in which the concentration of calcium ions in the plasma is greater than about 10.5 mg/dL in humans.

[0075] The term "symptomatic hypercalcemia" as used herein refers to symptoms associated with one of more of the signs or symptoms of hypercalcemia. Early manifestations of hypercalcemia include weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain, or metallic taste. Late manifestations include polydypsia, polyuria, weight loss, pancreatitis, photophobia, pruritis, renal dysfunction, aminotransferase elevation, hypertension, cardiac arrhythmias, psychosis, stupor, or coma. Methods to determine the concentration of calcium ions in blood plasma are generally within the capability of a person of ordinary skill in the art.

[0076] The term "severe symptomatic hypercalcemia" as used herein is referred to grade 3 or grade 4 toxic level of hypercalcemia as defined in U.S. Patent 6,521,608, which is incorporated by reference herein in its entirety. A grade 4 toxicity is associated with reduced count for WBC, platelets, hemoglobin, neutrophils and lymphocytes; massive hemorrhage; gastrointestinal problems (such as vomiting more than 10 times a day, diarrhea (>10 times a day) and stomatitis which requires IV nutrition); hepatic failures (such as elevated bilirubin and hepatic coma), kidney/bladder dysfunction; cardiovascular events (such as refractory congestive heart failure, acute myocardial infraction, dyspnea at rest and cardiac tamponade); neuralgic disorders (such as paralysis, coma, seizures, cerebellar necrosis, severe headaches, blindness, uncorrectable deafness and suicidal mood) and metabolic problems (such as hyperglycemia (blood glucose >500 mg/dL) with ketoacidosis). Although grade 3 toxicity is milder than grade 4 toxicity, it can be life threatening and is associated with reduced count for WBC, platelets, hemoglobin, neutrophils and lymphocytes; gross hemorrhage; gastrointestinal problems (such as vomiting 6-10 times a day, diarrhea (7-9 times a day) and

painful ulcers (patient could not eat)); hepatic failures (such as precoma and elevated bilirubin); cardiovascular events (such as mild congestive heart failure responsive to treatment, angina without infraction and symptomatic effusion); neurologic disorders (such as severe loss or impairment of neuro-sensory, severe cortical contusion, unrelenting headache and correctable hearing loss) and weight change.

[0077] In a preferred embodiment of the invention, the active vitamin D compound or mimic thereof has a reduced hypercalcemic effect as compared to vitamin D so that increased doses of the compound can be administered without inducing hypercalcemia in the animal. A reduced hypercalcemic effect is defined as an effect which is less than the hypercalcemic effect induced by administration of an equal dose of 1α,25-hydroxyvitamin D_3 (calcitriol). As an example, EB 1089 has a hypercalcemic effect which is 50% of the hypercalcemic effect of calcitriol. Additional active vitamin D compounds having a reduced hypercalcemic effect include Ro23-7553 and Ro24-5531 available from Hoffmann LaRoche. Other examples of active vitamin D compounds having a reduced hypercalcemic effect can be found in U.S. Patent No. 4,717,721. Determining the hypercalcemic effect of an active vitamin D compound is routine in the art and can be carried out as disclosed in Hansen *et al., Curr. Pharm. Des. 6*: 803-828 (2000).

[0078] In one embodiment of the invention, an active vitamin D compound is administered to an animal before, during and/or after chemotherapy. The active vitamin D compound can be administered 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, or more prior to the chemotherapy or radiotherapy. The active vitamin D compound can be administered 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, 4 weeks, or more after the chemotherapy or radiotherapy and continued for up to six months. In certain embodiments the active vitamin D compound is administered before, during, and after the chemotherapy or radiotherapy.

[0079] In one aspect of the invention, one or more therapeutic agents or treatments are administered to an animal in addition to the active vitamin D compound. The active vitamin D compound, or a mimic thereof, can be administered prior to (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 2 weeks, 3 weeks, 4 weeks or more), concurrently with, or after (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 2 weeks, 3 weeks, 4 weeks or more) the administration of one or more therapeutic agents or treatments.

[0080] In certain embodiments, the method of administering an active vitamin D compound, or a mimic thereof, in combination with one or more therapeutic agents or treatments may be repeated at least once. The method may be repeated as many times as necessary to achieve or maintain a therapeutic response, *e.g.*, from one to about ten times. With each repetition of the method the active vitamin D compound, or a mimic thereof, and the one or more therapeutic agents or treatments may be the same or different from that used in the previous repetition. Additionally, the time period of administration of the active vitamin D compound, or a mimic thereof, and the manner in which it is administered (*i.e.*, daily or HDPA) can vary from repetition to repetition.

[0081] When used, the one or more therapeutic agents or treatments are administered in doses known to one of skill in the art to prevent, treat, or ameliorate a pulmonary disorder. The one or more therapeutic agents or treatments are administered in pharmaceutical compositions and by methods known to be effective. For example, the therapeutic agents or treatments may be administered systemically (*e.g.*, intravenously, orally) or locally.

[0082] The doses of the vitamin D analogs and vitamin D mimics may be adjusted proportionate to the ratio of the efficacy index to the calcemic index according to the formula:

$$\text{Dose} = CalcitriolDose \times (EI \div CI)$$

where Dose is the analog or mimic dose, calcitriolDose is calcitriol dose, EI is the analog or mimic efficacy index and CI is the analog or

mimic calcemic index, wherein the term "efficacy index" is the ratio of the concentration of the vitamin D analog or mimic to the concentration of calcitriol at equivalent potency. Thus, the efficacy index is a fraction less than one when the vitamin D analog or mimic is less potent than calcitriol. EI is number greater than one when calcitriol is less potent than the vitamin D analog or mimic. The "calcemic index" of a drug is a measure of the relative ability of the drug to generate a calcemic response as reported in Bouillon et al., Endocrine Reviews 16:200-257, 1995. A calcemic index of 1 corresponds to the relative calcemic activity of calcitriol. A calcemic index of about 0.01 corresponds to the calcemic activity of a drug with approximately 100 times less calcemic activity than calcitriol. A calcemic index of 0.5 would correspond to a drug having approximately half the calcemic activity of calcitriol. The calcemic index of a drug can vary depending on the assay conducted, e.g. whether one is measuring stimulation of intestinal calcium absorption (a process by which dietary calcium enters into the physiological processes to contribute to the skeletal growth of the organism and to the maintenance of calcium homeostasis) or bone calcium mobilizing activity (a process by which the bone matrix acts as an exchangeable reservoir for calcium). See U.S. Patent 6,521,608 for further detail.

[0083] The active vitamin D compound or a mimic thereof is preferably administered at a dose of about 0.5 μg to about 300 μg, more preferably from about 15 μg to about 200 μg. In a specific embodiment, an effective amount of an active vitamin D compound or a mimic thereof is 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, or 300 μg or more. In certain embodiments, an effective dose of an active vitamin D compound or a mimic thereof is between about 3 μg to about 300 μg, more preferably between about 15 μg to about 260 μg, more preferably between about 30 μg to about 240 μg, more preferably between about 50 μg to about 220 μg, more preferably between about 75 μg to about 200 μg. In another embodiment, an effective amount of an active

vitamin D compound or a mimic thereof is about 300, 400, 500, 600, 700, 800, 900 μg, 1, 2, 3, 4 or 5 mg. In certain embodiments, an effective dose of an active vitamin D compound or a mimic thereof is between about 300 μg to about 5 mg, more preferably between about 500 μg and about 4 mg, more preferably between about 800 μg and about 3 mg, more preferably between about 1 and about 3 mg. In certain embodiments, the methods of the invention comprise administering an active vitamin D compound or a mimic thereof in a dose of about 0.12 μg/kg bodyweight to about 3 μg/kg bodyweight. The compound may be administered by any route, including oral, intramuscular, intravenous, parenteral, rectal, nasal, topical, or transdermal.

[0084] If the active vitamin D compound or a mimic thereof is to be administered daily, the dose may be kept low, for example about 0.5 μg to about 5 μg, in order to avoid or diminish the induction of hypercalcemia. If the active vitamin D compound or a mimic thereof has a reduced hypercalcemic effect a higher daily dose may be administered without resulting in hypercalcemia, for example about 10 μg to about 20 μg or higher (up to about 50 μg to about 100 μg).

[0085] In a preferred embodiment of the invention, the active vitamin D compound or a mimic thereof is administered by HDPA so that high doses of the active vitamin D compound or the mimic thereof can be administered without inducing hypercalcemia. HDPA refers to intermittently administering an active vitamin D compound, or a mimic thereof, on either a continuous intermittent dosing schedule or a non-continuous intermittent dosing schedule. High doses of active vitamin D compounds include doses greater than about 3 μg as discussed in the sections above. Therefore, in certain embodiments of the invention, the methods for the prevention, treatment, or amelioration of pulmonary disorders encompass intermittently administering high doses of active vitamin D compounds. The frequency of the HDPA can be limited by a number of factors including, but not limited to, the pharmacokinetic parameters of the compound or formulation and the pharmacodynamic effects of the active vitamin D compound, or a mimic thereof, on the animal. For example, animals having impaired renal function may require less frequent

administration of the active vitamin D compound or the mimic thereof because of the decreased ability of those animals to excrete calcium.

[0086] The following is exemplary only and merely serves to illustrate that the term HDPA can encompass any discontinuous administration regimen designed by a person of skill in the art.

[0087] In one example, the active vitamin D compound, or the mimic thereof, can be administered not more than once every three days, every four days, every five days, every six days, every seven days, every eight days, every nine days, or every ten days. The administration can continue for one, two, three, or four weeks or one, two, or three months, or longer. Optionally, after a period of rest, the active vitamin D compound, or the mimic thereof, can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the active vitamin D compound, or the mimic thereof, on the animal.

[0088] In another example, the active vitamin D compound or the mimic thereof can be administered once per week for three months.

[0089] In a preferred embodiment, the vitamin D compound or a mimic thereof can be administered once per week for three weeks of a four week cycle. After a one week period of rest, the active vitamin D compound or a mimic thereof can be administered under the same or different schedule.

[0090] Further examples of dosing schedules that can be used in the methods of the present invention are provided in U.S. Patent No. 6,521,608.

[0091] The above-described administration schedules are provided for illustrative purposes only and should not be considered limiting. A person of skill in the art will readily understand that all active vitamin D compounds, or mimics thereof, are within the scope of the invention and that the exact dosing and schedule of administration of the active vitamin D compounds or the mimics thereof can vary due to many factors.

[0092] The amount of a therapeutically effective dose of a pharmaceutical agent or treatment in the acute or chronic management of a disease or disorder may differ depending on factors including, but not limited to, the disease or disorder treated, the specific pharmaceutical agents or treatments and the route

of administration. According to the methods of the invention, an effective dose of an active vitamin D compound, or a mimic thereof, is any dose of the compound effective to prevent, treat, or ameliorate a pulmonary disorder. A high dose of an active vitamin D compound, or a mimic thereof, can be a dose from about 3 μg to about 300 μg or any dose within this range as discussed above. The dose, dose frequency, duration, or any combination thereof, may also vary according to age, body weight, response, and the past medical history of the animal as well as the route of administration, pharmacokinetics, and pharmacodynamic effects of the pharmaceutical agents or treatments. These factors are routinely considered by one of skill in the art.

[0093] The rate of absorption and clearance of vitamin D compounds and mimics thereof are affected by a variety of factors that are well known to persons of skill in the art. As discussed above, the pharmacokinetic properties of active vitamin D compounds and mimics thereof limit the peak concentration of vitamin D compounds and mimics thereof that can be obtained in the blood without inducing the onset of hypercalcemia. The rate and extent of absorption, distribution, binding or localization in tissues, biotransformation, and excretion of the active vitamin D compound or a mimic thereof can all affect the frequency at which the pharmaceutical agents or treatments can be administered.

[0094] In one embodiment of the invention, an active vitamin D compound or a mimic thereof is administered at a dose sufficient to achieve peak plasma concentrations of the active vitamin D compound, or the mimic thereof, of about 0.1 nM to about 25 nM. In certain embodiments, the methods of the invention comprise administering the active vitamin D compound, or the mimic thereof, in a dose that achieves peak plasma concentrations of 0.1 nM, 0.2 nM, 0.3 nM, 0.4 nM, 0.5 nM, 0.6 nM, 0.7 nM, 0.8 nM, 0.9 nM, 1 nM, 2 nM, 3 nM, 4 nM, 5 nM, 6 nM, 7 nM, 8 nM, 9 nM, 10 nM, 12.5 nM, 15 nM, 17.5 nM, 20 nM, 22.5 nM, or 25 nM or any range of concentrations therein. In other embodiments, the active vitamin D compound, or the mimic thereof, is administered in a dose that achieves peak plasma concentrations of the active vitamin D compound, or the mimic thereof, exceeding about 0.5 nM,

preferably about 0.5 nM to about 25 nM, more preferably about 5 nM to about 20 nM, and even more preferably about 10 nM to about 15 nM.

[0095] In another preferred embodiment, the active vitamin D compound, or a mimic thereof, is administered at a dose of at least about 0.12 μg/kg bodyweight, more preferably at a dose of at least about 0.5 μg/kg bodyweight.

[0096] One of skill in the art will recognize that these standard doses are for an average sized adult of approximately 70 kg and can be adjusted for the factors routinely considered as stated above.

[0097] In certain embodiments, the methods of the invention further comprise administering a dose of an active vitamin D compound, or a mimic thereof, that achieves peak plasma concentrations rapidly, *e.g.*, within four hours. In further embodiments, the methods of the invention comprise administering a dose of an active vitamin D compound, or a mimic thereof, that is eliminated quickly, *e.g.*, with an elimination half-life of less than 12 hours.

[0098] While obtaining high concentrations of the active vitamin D compound, or a mimic thereof, is beneficial, it must be balanced with clinical safety, *e.g.*, hypercalcemia. Thus, in one aspect of the invention, the methods of the invention encompass HDPA of active vitamin D compounds, or mimics thereof, to an animal before, during, or after chemotherapy or radiotherapy and monitoring the animal for symptoms associated with hypercalcemia. Such symptoms include calcification of soft tissues (*e.g.*, cardiac tissue), increased bone density, and hypercalcemic nephropathy. In still another embodiment, the methods of the invention encompass HDPA of an active vitamin D compound, or a mimic thereof, to an animal before, during, or after chemotherapy or radiotherapy and monitoring the calcium plasma concentration of the animal to ensure that the calcium plasma concentration is less than about 10.2 mg/dL.

[0099] In certain embodiments, high blood levels of vitamin D compounds can be safely obtained in conjunction with reducing the transport of calcium into the blood. In one embodiment, higher active vitamin D compound concentrations are safely obtainable without the onset of hypercalcemia when

administered in conjunction with a reduced calcium diet. In one example, the calcium can be trapped by an adsorbent, absorbent, ligand, chelate, or other binding moiety that cannot be transported into the blood through the small intestine. In another example, the rate of osteoclast activation can be inhibited by administering, for example, a bisphosphonate such as, *e.g.*, zoledronate, pamidronate, or alendronate, or a corticosteroid such as, *e.g.*, dexamethasone or prednisone, in conjunction with the active vitamin D compound, or a mimic thereof,.

[00100] In certain embodiments, high blood levels of active vitamin D compounds are safely obtained in conjunction with maximizing the rate of clearance of calcium. In one example, calcium excretion can be increased by ensuring adequate hydration and salt intake. In another example, diuretic therapy can be used to increase calcium excretion.

[00101] The active vitamin D compound or a mimic thereof may be administered as part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier, wherein the active vitamin D compound or a mimic thereof is present in an amount which is effective to achieve its intended purpose, *i.e.*, to have the desired effect of preventing, treating or ameliorating a pulmonary disorder in a patient receiving chemotherapy or radiotherapy. The pharmaceutical composition may further comprise one or more excipients, diluents or any other components known to persons of skill in the art and germane to the methods of formulation of the present invention. The pharmaceutical composition may additionally comprise other compounds typically used as adjuncts during prevention, treatment, or amelioration of pulmonary disorders.

[00102] The term "pharmaceutical composition" as used herein is to be understood as defining compositions of which the individual components or ingredients are themselves pharmaceutically acceptable, *e.g.*, where oral administration is foreseen, acceptable for oral use and, where topical administration is foreseen, topically acceptable.

[00103] The pharmaceutical composition can be prepared in single unit dosage forms. The dosage forms are suitable for oral, mucosal (nasal, sublingual,

vaginal, buccal, rectal), parenteral (intravenous, intramuscular, intraarterial), or topical administration. Preferred dosage forms of the present invention include oral dosage forms and intravenous dosage forms.

[00104] Intravenous forms include, but are not limited to, bolus and drip injections. In preferred embodiments, the intravenous dosage forms are sterile or capable of being sterilized prior to administration to a subject since they typically bypass the subject's natural defenses against contaminants. Examples of intravenous dosage forms include, but are not limited to, Water for Injection USP; aqueous vehicles including, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles including, but not limited to, ethyl alcohol, polyethylene glycol and polypropylene glycol; and non-aqueous vehicles including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate and benzyl benzoate.

[00105] In a preferred embodiment of the invention, the pharmaceutical compositions comprising active vitamin D compounds, or a mimic thereof, are emulsion pre-concentrate formulations. The compositions of the invention meet or substantially reduce the difficulties associated with active vitamin D compound therapy or a mimic thereof hitherto encountered in the art including, in particular, undesirable pharmacokinetic parameters of the compound upon administration to a patient.

[00106] According to one aspect of the present invention, a pharmaceutical composition is provided comprising (a) a lipophilic phase component, (b) one or more surfactants, (c) an active vitamin D compound, or a mimic thereof; wherein said composition is an emulsion pre-concentrate, which upon dilution with water, in a water to composition ratio of about 1:1 or more of said water, forms an emulsion having an absorbance of greater than 0.3 at 400 nm. The pharmaceutical composition of the invention may further comprise a hydrophilic phase component.

[00107] In another aspect of the invention, a pharmaceutical emulsion composition is provided comprising water (or other aqueous solution) and an emulsion pre-concentrate.

[00108] The term "emulsion pre-concentrate," as used herein, is intended to mean a system capable of providing an emulsion upon contacting with, *e.g.*, water. The term "emulsion," as used herein, is intended to mean a colloidal dispersion comprising water and organic components including hydrophobic (lipophilic) organic components. The term "emulsion" is intended to encompass both conventional emulsions, as understood by those skilled in the art, as well as "sub-micron droplet emulsions," as defined immediately below.

[00109] The term "sub-micron droplet emulsion," as used herein is intended to mean a dispersion comprising water and organic components including hydrophobic (lipophilic) organic components, wherein the droplets or particles formed from the organic components have an average maximum dimension of less than about 1000 nm.

[00110] Sub-micron droplet emulsions are identifiable as possessing one or more of the following characteristics. They are formed spontaneously or substantially spontaneously when their components are brought into contact, that is without substantial energy supply, *e.g.*, in the absence of heating or the use of high shear equipment or other substantial agitation. They exhibit thermodynamic stability and they are monophasic.

[00111] The particles of a sub-micron droplet emulsion may be spherical, though other structures are feasible, *e.g.* liquid crystals with lamellar, hexagonal or isotropic symmetries. Generally, sub-micron droplet emulsions comprise droplets or particles having a maximum dimension (*e.g.*, average diameter) of between about 50 nm to about 1000 nm, and preferably between about 200 nm to about 300 nm.

[00112] The pharmaceutical compositions of the present invention will generally form an emulsion upon dilution with water. The emulsion will form according to the present invention upon the dilution of an emulsion pre-concentrate with water in a water to composition ratio of about 1:1 or more of said water. According to the present invention, the ratio of water to

composition can be, *e.g.*, between 1:1 and 5000:1. For example, the ratio of water to composition can be about 1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 200:1, 300:1, 500:1, 1000:1, or 5000:1. The skilled artisan will be able to readily ascertain the particular ratio of water to composition that is appropriate for any given situation or circumstance.

[00113] According to the present invention, upon dilution of said emulsion pre-concentrate with water, an emulsion will form having an absorbance of greater than 0.3 at 400 nm. The absorbance at 400 nm of the emulsions formed upon 1:100 dilution of the emulsion pre-concentrates of the present invention can be, *e.g.*, between 0.3 and 4.0. For example, the absorbance at 400 nm can be about 0.4, 0.5, 0.6, 1.0, 1.2, 1.6, 2.0, 2.2, 2.4, 2.5, 3.0, or 4.0. Methods for determining the absorbance of a liquid solution are well known by those in the art. The skilled artisan will be able to ascertain and adjust the relative proportions of the ingredients of the emulsion pre-concentrates of the invention in order to obtain, upon dilution with water, an emulsion having any particular absorbance encompassed within the scope of the invention.

[00114] The pharmaceutical compositions of the present invention can be, *e.g.*, in a solid, semi-solid, or liquid formulation. Semi-solid formulations of the present invention can be any semi-solid formulation known by those of ordinary skill in the art, including, *e.g.*, gels, pastes, creams and ointments.

[00115] The pharmaceutical compositions of the present invention comprise a lipophilic phase component. Suitable components for use as lipophilic phase components include any pharmaceutically acceptable solvent which is non-miscible with water. Such solvents will appropriately be devoid or substantially devoid of surfactant function.

[00116] The lipophilic phase component may comprise mono-, di- or triglycerides. Mono-, di- and triglycerides that may be used within the scope of the invention include those that are derived from C_6, C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20} and C_{22} fatty acids. Exemplary diglycerides include, in particular, diolein, dipalmitolein, and mixed caprylin-caprin diglycerides. Preferred triglycerides include vegetable oils, fish oils, animal fats, hydrogenated vegetable oils, partially hydrogenated vegetable oils, synthetic triglycerides,

modified triglycerides, fractionated triglycerides, medium and long-chain triglycerides, structured triglycerides, and mixtures thereof.

[00117] Among the above-listed triglycerides, preferred triglycerides include: almond oil; babassu oil; borage oil; blackcurrant seed oil; canola oil; castor oil; coconut oil; corn oil; cottonseed oil; evening primrose oil; grapeseed oil; groundnut oil; mustard seed oil; olive oil; palm oil; palm kernel oil; peanut oil; rapeseed oil; safflower oil; sesame oil; shark liver oil; soybean oil; sunflower oil; hydrogenated castor oil; hydrogenated coconut oil; hydrogenated palm oil; hydrogenated soybean oil; hydrogenated vegetable oil; hydrogenated cottonseed and castor oil; partially hydrogenated soybean oil; partially soy and cottonseed oil; glyceryl tricaproate; glyceryl tricaprylate; glyceryl tricaprate; glyceryl triundecanoate; glyceryl trilaurate; glyceryl trioleate; glyceryl trilinoleate; glyceryl trilinolenate; glyceryl tricaprylate/caprate; glyceryl tricaprylate/caprate/laurate; glyceryl tricaprylate/caprate/linoleate; and glyceryl tricaprylate/caprate/stearate.

[00118] A preferred triglyceride is the medium chain triglyceride available under the trade name LABRAFAC CC. Other preferred triglycerides include neutral oils, *e.g.*, neutral plant oils, in particular fractionated coconut oils such as known and commercially available under the trade name MIGLYOL, including the products: MIGLYOL 810; MIGLYOL 812; MIGLYOL 818; and CAPTEX 355.

[00119] Also suitable are caprylic-capric acid triglycerides such as known and commercially available under the trade name MYRITOL, including the product MYRITOL 813. Further suitable products of this class are CAPMUL MCT, CAPTEX 200, CAPTEX 300, CAPTEX 800, NEOBEE M5 and MAZOL 1400.

[00120] Especially preferred as lipophilic phase component is the product MIGLYOL 812. (*See* U.S. Patent No. 5,342,625).

[00121] Pharmaceutical compositions of the present invention may further comprise a hydrophilic phase component. The hydrophilic phase component may comprise, *e.g.*, a pharmaceutically acceptable C_{1-5} alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or

poly-oxy-alkanediol. Suitable hydrophilic phase components include, *e.g.*, di- or partial-, especially partial-, -ethers of mono- or poly-, especially mono- or di-, -oxy-alkanediols comprising from 2 to 12, especially 4 carbon atoms. Preferably the mono- or poly-oxy-alkanediol moiety is straight-chained. Exemplary hydrophilic phase components for use in relation to the present invention are those known and commercially available under the trade names TRANSCUTOL and COLYCOFUROL. (*See* U.S. Patent No. 5,342,625).

[00122] In an especially preferred embodiment, the hydrophilic phase component comprises 1,2-propyleneglycol.

[00123] The hydrophilic phase component of the present invention may of course additionally include one or more additional ingredients. Preferably, however, any additional ingredients will comprise materials in which the active vitamin D compound or a mimic thereof is sufficiently soluble, such that the efficacy of the hydrophilic phase as a carrier medium for active vitamin D compound or a mimic thereof is not materially impaired. Examples of possible additional hydrophilic phase components include lower (*e.g.*, C_{1-5}) alkanols, in particular ethanol.

[00124] Pharmaceutical compositions of the present invention also comprise one or more surfactants. Surfactants that can be used in conjunction with the present invention include hydrophilic or lipophilic surfactants, or mixtures thereof. Especially preferred are non-ionic hydrophilic and non-ionic lipophilic surfactants.

[00125] Suitable hydrophilic surfactants include reaction products of natural or hydrogenated vegetable oils and ethylene glycol, *i.e.* polyoxyethylene glycolated natural or hydrogenated vegetable oils, for example polyoxyethylene glycolated natural or hydrogenated castor oils. Such products may be obtained in known manner, *e.g.*, by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, *e.g.*, in a molar ratio of from about 1:35 to about 1:60, with optional removal of free polyethyleneglycol components from the product, *e.g.*, in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819.

[00126] Suitable hydrophilic surfactants for use in the present pharmaceutical compounds also include polyoxyethylene-sorbitan-fatty acid esters, *e.g.*, mono- and trilauryl, palmityl, stearyl and oleyl esters, *e.g.*, of the type known and commercially available under the trade name TWEEN; including the products:

TWEEN 20 (polyoxyethylene(20)sorbitanmonolaurate),
TWEEN 40 (polyoxyethylene(20)sorbitanmonopalmitate),
TWEEN 60 (polyoxyethylene(20)sorbitanmonostearate),
TWEEN 80 (polyoxyethylene(20)sorbitanmonooleate),
TWEEN 65 (polyoxyethylene(20)sorbitantristearate),
TWEEN 85 (polyoxyethylene(20)sorbitantrioleate),
TWEEN 21 (polyoxyethylene(4)sorbitanmonolaurate),
TWEEN 61 (polyoxyethylene(4)sorbitanmonostearate), and
TWEEN 81 (polyoxyethylene(5)sorbitanmonooleate).

[00127] Especially preferred products of this class for use in the compositions of the invention are the above products TWEEN 40 and TWEEN 80. (*See* Hauer, *et al.*, U.S. Patent No. 5,342,625).

[00128] Also suitable as hydrophilic surfactants for use in the present pharmaceutical compounds are polyoxyethylene alkylethers; polyoxyethylene glycol fatty acid esters, for example polyoxyethylene stearic acid esters; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and, *e.g.*, fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; polyoxyethylene-polyoxypropylene co-polymers; polyoxyethylene-polyoxypropylene block co-polymers; dioctylsuccinate, dioctylsodiumsulfosuccinate, di-[2-ethylhexyl]-succinate or sodium lauryl sulfate; phospholipids, in particular lecithins such as, *e.g.*, soya bean lecithins; propylene glycol mono- and di-fatty acid esters such as, *e.g.*, propylene glycol dicaprylate, propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate, and, especially preferred, propylene

glycol caprylic-capric acid diester; and bile salts, *e.g.*, alkali metal salts, for example sodium taurocholate.

[00129] Suitable lipophilic surfactants include alcohols; polyoxyethylene alkylethers; fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid esters of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; trans-esterified vegetable oils; sterols; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

[00130] Suitable lipophilic surfactants for use in the present pharmaceutical compounds also include trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols. Such trans-esterification products are known in the art and may be obtained *e.g.*, in accordance with the general procedures described in U.S. Patent No. 3,288,824. They include trans-esterification products of various natural (*e.g.*, non-hydrogenated) vegetable oils for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil and palm oil and mixtures thereof with polyethylene glycols, in particular polyethylene glycols having an average molecular weight of from 200 to 800. Preferred are products obtained by trans-esterification of 2 molar parts of a natural vegetable oil triglyceride with one molar part of polyethylene glycol (*e.g.*, having an average molecular weight of from 200 to 800). Various forms of trans-esterification products of the defined class are known and commercially available under the trade name LABRAFIL.

[00131] Additional lipophilic surfactants that are suitable for use with the present pharmaceutical compositions include oil-soluble vitamin derivatives, *e.g.*, tocopherol PEG-1000 succinate ("vitamin E TPGS").

[00132] Also suitable as lipophilic surfactants for use in the present pharmaceutical compounds are mono-, di- and mono/di-glycerides, especially esterification products of caprylic or capric acid with glycerol; sorbitan fatty acid esters; pentaerythritol fatty acid esters and polyalkylene glycol ethers, for example pentaerythrite- -dioleate, -distearate, -monolaurate, -polyglycol ether and -monostearate as well as pentaerythrite-fatty acid esters; monoglycerides, *e.g.*, glycerol monooleate, glycerol monopalmitate and glycerol monostearate; glycerol triacetate or (1,2,3)-triacetin; and sterols and derivatives thereof, for example cholesterols and derivatives thereof, in particular phytosterols, *e.g.*, products comprising sitosterol, campesterol or stigmasterol, and ethylene oxide adducts thereof, for example soya sterols and derivatives thereof.

[00133] It is understood by those of ordinary skill in the art that several commercial surfactant compositions contain small to moderate amounts of triglycerides, typically as a result of incomplete reaction of a triglyceride starting material in, for example, a trans-esterification reaction. Thus, the surfactants that are suitable for use in the present pharmaceutical compositions include those surfactants that contain a triglyceride. Examples of commercial surfactant compositions containing triglycerides include some members of the surfactant families GELUCIRES, MAISINES, and IMWITORS. Specific examples of these compounds are GELUCIRE 44/14 (saturated polyglycolized glycerides); GELUCIRE 50/13 (saturated polyglycolized glycerides); GELUCIRE 53/10 (saturated polyglycolized glycerides); GELUCIRE 33/01 (semi-synthetic triglycerides of C_8-C_{18} saturated fatty acids); GELUCIRE 39/01 (semi-synthetic glycerides); other GELUCIRES, such as 37/06, 43/01, 35/10, 37/02, 46/07, 48/09, 50/02, 62/05, *etc.*; MAISINE 35-I (linoleic glycerides); and IMWITOR 742 (caprylic/capric glycerides). (*See* U.S. Patent No. 6,267,985).

[00134] Still other commercial surfactant compositions having significant triglyceride content are known to those skilled in the art. It should be appreciated that such compositions, which contain triglycerides as well as surfactants, may be suitable to provide all or part of the lipophilic phase

component of the of the present invention, as well as all or part of the surfactants.

[00135] The relative proportion of ingredients in the compositions of the invention will, of course, vary considerably depending on the particular type of composition concerned. The relative proportions will also vary depending on the particular function of ingredients in the composition. The relative proportions will also vary depending on the particular ingredients employed and the desired physical characteristics of the product composition, *e.g.*, in the case of a composition for topical use, whether this is to be a free flowing liquid or a paste. Determination of workable proportions in any particular instance will generally be within the capability of a person of ordinary skill in the art. All indicated proportions and relative weight ranges described below are accordingly to be understood as being indicative of preferred or individually inventive teachings only and not as limiting the invention in its broadest aspect.

[00136] The lipophilic phase component of the invention will suitably be present in an amount of from about 30% to about 90% by weight based upon the total weight of the composition. Preferably, the lipophilic phase component is present in an amount of from about 50% to about 85% by weight based upon the total weight of the composition.

[00137] The surfactant or surfactants of the invention will suitably be present in an amount of from about 1% to 50% by weight based upon the total weight of the composition. Preferably, the surfactant(s) is present in an amount of from about 5% to about 40% by weight based upon the total weight of the composition.

[00138] The amount of active vitamin D compound or a mimic thereof in compositions of the invention will of course vary, *e.g.*, depending on the intended route of administration and to what extent other components are present. In general, however, the active vitamin D compound or a mimic thereof of the invention will suitably be present in an amount of from about 0.005% to 20% by weight based upon the total weight of the composition. Preferably, the active vitamin D compound or a mimic thereof, is present in an

amount of from about 0.01% to 15% by weight based upon the total weight of the composition.

[00139] The hydrophilic phase component of the invention will suitably be present in an amount of from about 2% to about 20% by weight based upon the total weight of the composition. Preferably, the hydrophilic phase component is present in an amount of from about 5% to 15% by weight based upon the total weight of the composition.

[00140] The pharmaceutical composition of the invention may be in a semisolid formulation. Semisolid formulations within the scope of the invention may comprise, *e.g.*, a lipophilic phase component present in an amount of from about 60% to about 80% by weight based upon the total weight of the composition, a surfactant present in an amount of from about 5% to about 35% by weight based upon the total weight of the composition, and an active vitamin D compound or a mimic thereof, present in an amount of from about 0.01% to about 15% by weight based upon the total weight of the composition.

[00141] The pharmaceutical compositions of the invention may be in a liquid formulation. Liquid formulations within the scope of the invention may comprise, *e.g.*, a lipophilic phase component present in an amount of from about 50% to about 60% by weight based upon the total weight of the composition, a surfactant present in an amount of from about 4% to about 25% by weight based upon the total weight of the composition, an active vitamin D compound or a mimic thereof present in an amount of from about 0.01% to about 15% by weight based upon the total weight of the composition, and a hydrophilic phase component present in an amount of from about 5% to about 10% by weight based upon the total weight of the composition.

[00142] Additional compositions that may be used include the following, wherein the percentage of each component is by weight based upon the total weight of the composition excluding the active vitamin D compound or a mimic thereof,:

a.	Gelucire 44/14	about 50%
	Miglyol 812	about 50%;

b.	Gelucire 44/14	about 50%
	Vitamin E TPGS	about 10%
	Miglyol 812	about 40%;
c.	Gelucire 44/14	about 50%
	Vitamin E TPGS	about 20%
	Miglyol 812	about 30%;
d.	Gelucire 44/14	about 40%
	Vitamin E TPGS	about 30%
	Miglyol 812	about 30%;
e.	Gelucire 44/14	about 40%
	Vitamin E TPGS	about 20%
	Miglyol 812	about 40%;
f.	Gelucire 44/14	about 30%
	Vitamin E TPGS	about 30%
	Miglyol 812	about 40%;
g.	Gelucire 44/14	about 20%
	Vitamin E TPGS	about 30%
	Miglyol 812	about 50%;
h.	Vitamin E TPGS	about 50%
	Miglyol 812	about 50%;
i.	Gelucire 44/14	about 60%
	Vitamin E TPGS	about 25%
	Miglyol 812	about 15%;

j.	Gelucire 50/13	about 30%
	Vitamin E TPGS	about 5%
	Miglyol 812	about 65%;
k.	Gelucire 50/13	about 50%
	Miglyol 812	about 50%;
l.	Gelucire 50/13	about 50%
	Vitamin E TPGS	about 10%
	Miglyol 812	about 40%;
m.	Gelucire 50/13	about 50%
	Vitamin E TPGS	about 20%
	Miglyol 812	about 30%;
n.	Gelucire 50/13	about 40%
	Vitamin E TPGS	about 30%
	Miglyol 812	about 30%;
o.	Gelucire 50/13	about 40%
	Vitamin E TPGS	about 20%
	Miglyol 812	about 40%;
p.	Gelucire 50/13	about 30%
	Vitamin E TPGS	about 30%
	Miglyol 812	about 40%;
q.	Gelucire 50/13	about 20%
	Vitamin E TPGS	about 30%
	Miglyol 812	about 50%;
r.	Gelucire 50/13	about 60%

	Vitamin E TPGS	about 25%
	Miglyol 812	about 15%;
s.	Gelucire 44/14	about 50%
	PEG 4000	about 50%;
t.	Gelucire 50/13	about 50%
	PEG 4000	about 50%;
u.	Vitamin E TPGS	about 50%
	PEG 4000	about 50%;
v.	Gelucire 44/14	about 33.3%
	Vitamin E TPGS	about 33.3%
	PEG 4000	about 33.3%;
w.	Gelucire 50/13	about 33.3%
	Vitamin E TPGS	about 33.3%
	PEG 4000	about 33.3%;
x.	Gelucire 44/14	about 50%
	Vitamin E TPGS	about 50%;
y.	Gelucire 50/13	about 50%
	Vitamin E TPGS	about 50%;
z.	Vitamin E TPGS	about 5%
	Miglyol 812	about 95%;
aa.	Vitamin E TPGS	about 5%
	Miglyol 812	about 65%
	PEG 4000	about 30%;

ab.	Vitamin E TPGS	about 10%
	Miglyol 812	about 90%;
ac.	Vitamin E TPGS	about 5%
	Miglyol 812	about 85%
	PEG 4000	about 10%; and
ad.	Vitamin E TPGS	about 10%
	Miglyol 812	about 80%
	PEG 4000	about 10%.

[00143] In one embodiment of the invention, the pharmaceutical compositions comprise an active vitamin D compound or a mimic thereof, a lipophilic component, and a surfactant. The lipophilic component may be present in any percentage from about 1% to about 100%. The lipophilic component may be present at about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%. The surfactant may be present in any percentage from about 1% to about 100%. The surfactant may be present at about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%. In one embodiment, the lipophilic component is MIGLYOL 812 and the surfactant is vitamin E TPGS. In preferred embodiments, the pharmaceutical compositions comprise 50% MIGLYOL 812 and 50% vitamin E TPGS, 90% MIGLYOL 812 and 10% vitamin E TPGS, or 95% MIGLYOL 812 and 5% vitamin E TPGS.

[00144] In another embodiment of the invention, the pharmaceutical compositions comprise an active vitamin D compound and a lipophilic component, *e.g.*, around 100% MIGLYOL 812.

[00145] In a preferred embodiment, the pharmaceutical compositions comprise 50% MIGLYOL 812, 50% vitamin E TPGS, and small amounts of BHA and BHT. This formulation has been shown to be unexpectedly stable, both chemically and physically (see Example 3). The enhanced stability provides the compositions with a longer shelf life. Importantly, the stability also allows the compositions to be stored at room temperature, thereby avoiding the complication and cost of storage under refrigeration. Additionally, this composition is suitable for oral administration and has been shown to be capable of solubilizing high doses of active vitamin D compound, thereby enabling high dose pulse administration of active vitamin D compounds for the treatment of hyperproliferative diseases and other disorders.

[00146] In certain embodiments, the pharmaceutical compositions comprise about 50% MIGLYOL 812, about 50% vitamin E TPGS, and about 0.01% to about 0.50% each of BHA and BHT. In other embodiments, the pharmaceutical compositions comprise about 50% MIGLYOL 812, about 50% vitamin E TPGS, and about 0.05% to about 0.35% each of BHA and BHT. In certain embodiments, the pharmaceutical compositions comprise about 50% MIGLYOL 812, about 50% vitamin E TPGS, about 0.35% BHA, and about 0.10% BHT.

[00147] Additional compositions that may be used include the following, wherein the percentage of each component is by weight based upon the total weight of the composition excluding the active vitamin D compound or a mimic thereof:

a.	Miglyol 812	about 100%
	BHA	about 0.05%
	BHT	about 0.05%;
b.	Miglyol 812	about 100%

	BHA	about 0.35%
	BHT	about 0.10%;
c.	Miglyol 812	about 50%
	Vitamin E TPGS	about 50%
	BHA	about 0.05%
	BHT	about 0.05%;
d.	Miglyol 812	about 50%
	Vitamin E TPGS	about 50%
	BHT	about 0.10%;
e.	Miglyol 812	about 50%
	Vitamin E TPGS	about 50%
	BHA	about 0.35%;
f.	Miglyol 812	about 50%
	Vitamin E TPGS	about 50%
	BHA	about 0.35%
	BHT	about 0.10%; and
g.	Miglyol 812	about 50%
	Vitamin E TPGS	about 50%
	BHA	about 0.28%
	BHT	about 0.08%.

[00148] It will be understood by those of skill in the art that the formulations of the invention comprising a lipophilic component and a surfactant in amounts that total about 100% (*e.g.*, about 50% lipophilic component and about 50% surfactant) provide adequate room for the active vitamin D compound and additives (*e.g.*, antioxidants) which are present in the formulation in small amounts, each generally present at less than 1% by weight.

[00149] The pharmaceutical compositions comprising the active vitamin D compound of the present invention may further comprise one or more additives. Additives that are well known in the art include, *e.g.*, detackifiers, anti-foaming agents, buffering agents, antioxidants (*e.g.*, ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols, *e.g.*, α-tocopherol (vitamin E)), preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired. For example, antioxidants may be present in an amount of from about 0.05% to about 0.35% by weight based upon the total weight of the composition.

[00150] The additive may also comprise a thickening agent. Suitable thickening agents may be those known and employed in the art, including, *e.g.*, pharmaceutically acceptable polymeric materials and inorganic thickening agents. Exemplary thickening agents for use in the present pharmaceutical compositions include polyacrylate and polyacrylate co-polymer resins, for example poly-acrylic acid and poly-acrylic acid/methacrylic acid resins; celluloses and cellulose derivatives including: alkyl celluloses, *e.g.*, methyl-, ethyl- and propyl-celluloses; hydroxyalkyl-celluloses, *e.g.*, hydroxypropyl-celluloses and hydroxypropylalkyl-celluloses such as hydroxypropyl-methyl-celluloses; acylated celluloses, *e.g.*, cellulose-acetates, cellulose-acetatephthallates, cellulose-acetatesuccinates and hydroxypropylmethyl-cellulose phthallates; and salts thereof such as sodium-carboxymethyl-celluloses; polyvinylpyrrolidones, including for example poly-N-vinylpyrrolidones and vinylpyrrolidone co-polymers such as vinylpyrrolidone-vinylacetate co-polymers; polyvinyl resins, *e.g.*, including polyvinylacetates and alcohols, as well as other polymeric materials including gum traganth, gum arabicum, alginates, *e.g.*, alginic acid, and salts thereof, *e.g.*, sodium alginates; and inorganic thickening agents such as atapulgite, bentonite and silicates including hydrophilic silicon dioxide products, *e.g.*, alkylated (for

example methylated) silica gels, in particular colloidal silicon dioxide products.

[00151] Such thickening agents as described above may be included, *e.g.*, to provide a sustained release effect. However, where oral administration is intended, the use of thickening agents as aforesaid will generally not be required and is generally less preferred. Use of thickening agents is, on the other hand, indicated, *e.g.*, where topical application is foreseen.

[00152] Compositions in accordance with the present invention may be employed for administration in any appropriate manner, *e.g.*, orally, *e.g.*, in unit dosage form, for example in a solution, in hard or soft encapsulated form including gelatin encapsulated form, parenterally or topically, *e.g.*, for application to the skin, for example in the form of a cream, paste, lotion, gel, ointment, poultice, cataplasm, plaster, dermal patch or the like, as a coating for a medical device, *e.g.*, a stent, or for ophthalmic application, for example in the form of an eye-drop, -lotion or -gel formulation. Readily flowable forms, for example solutions and emulsions, may also be employed *e.g.*, for intralesional injection, or may be administered rectally, *e.g.*, as an enema.

[00153] When the composition of the present invention is formulated in unit dosage form, the active vitamin D compound will preferably be present in an amount of between 1 and 200 μg per unit dose. More preferably, the amount of active vitamin D compound per unit dose will be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 μg or any amount therein. In a preferred embodiment, the amount of active vitamin D compound per unit dose will be about 5 μg to about 180 μg, more preferably about 10 μg to about 135 μg, more preferably about 45 μg. In one embodiment, the unit dosage form comprises 45, 90, 135, or 180 μg of calcitriol.

[00154] When the unit dosage form of the composition is a capsule, the total quantity of ingredients present in the capsule is preferably about 10-1000 μL. More preferably, the total quantity of ingredients present in the capsule is about 100-300 μL. In another embodiment, the total quantity of ingredients

present in the capsule is preferably about 10-1500 mg, preferably about 100-1000 mg. In one embodiment, the total quantity is about 225, 450, 675, or 900 mg. In one embodiment, the unit dosage form is a capsule comprising 45, 90, 135, or 180 μg of calcitriol.

[00155] Animals which may be treated according to the present invention include all animals which may benefit from administration of the compounds of the present invention. Such animals include humans, pets such as dogs and cats, and veterinary animals such as cows, pigs, sheep, goats and the like.

[00156] The following examples are illustrative, but not limiting, of the methods of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in medical treatment and pharmaceutical science and which are obvious to those skilled in the art are within the spirit and scope of the invention.

EXAMPLE 1

PREPARATION OF SEMI-SOLID CALCITRIOL FORMULATIONS

[00157] Five semi-solid calcitriol formulations (SS1-SS5) were prepared containing the ingredients listed in Table 1. The final formulation contains 0.208 mg calcitriol per gram of semi-solid formulation.

TABLE 1: Composition of Semi-Solid Calcitriol Formulation

Ingredients	SS1	SS2	SS3	SS4	SS5
Calcitriol	0.0208	0.0208	0.0208	0.0208	0.0208
Miglyol 812	80.0	0	65.0	0	79.0
Captex 200	0	82.0	0	60.0	0
Labrafac CC	0	0	0	0	12.0
Vitamin-E TPGS	20.0	18.0	5.0	5.0	9.0
Labrifil M	0	0	0	0	0
Gelucire 44/14	0	0	30.0	35.0	0
BHT	0.05	0.05	0.05	0.05	0.05
BHA	0.05	0.05	0.05	0.05	0.05

Amounts shown are in grams.

1. Preparation of Vehicles

[00158] One hundred gram quantities of the five semi-solid calcitriol formulations (SS1-SS5) listed in Table 1 were prepared as follows.

[00159] The listed ingredients, except for calcitriol, were combined in a suitable glass container and mixed until homogenous. Vitamin E TPGS and GELUCIRE 44/14 were heated and homogenized at 60°C prior to weighing and adding into the formulation.

2. Preparation of Active Formulations

[00160] The semi-solid vehicles were heated and homogenized at $\leq$ 60°C. Under subdued light, 12 $\pm$ 1 mg of calcitriol was weighed out into separate glass bottles with screw caps, one bottle for each formulation. (Calcitriol is light sensitive; subdued light/red light should be used when working with calcitriol/calcitriol formulations.) The exact weight was recorded to 0.1 mg.

The caps were then placed on the bottles as soon as the calcitriol had been placed into the bottles. Next, the amount of each vehicle required to bring the concentration to 0.208 mg/g was calculated using the following formula:

$C_w/0.208$ = required weight of vehicle
Where C_w = weight of calcitriol, in mg, and
0.208 = final concentration of calcitriol (mg/g).

[00161] Finally, the appropriate amount of each vehicle was added to the respective bottle containing the calcitriol. The formulations were heated (≤ 60°C) while being mixed to dissolve the calcitriol.

EXAMPLE 2

PREPARATION OF ADDITIONAL FORMULATIONS

[00162] Following the method of Example 1, twelve different formulations for calcitriol were prepared containing the ingredients listed in Table 2.

TABLE 2: Composition Formulations

Ingred-Ients	1	2	3	4	5	6	7	8	9	10	11	12
Miglyol 812N	95	65	90	85	80	95	65	90	85	80	50	0
Vitamin E TPGS	5	5	10	5	10	5	5	10	5	10	50	50
PEG 4000	0	30	0	10	10	0	30	0	10	10	0	50
BHA	0.05	0.05	0.05	0.05	0.05	0.35	0.35	0.35	0.35	0.35	0.35	0.35
BHT	0.05	0.05	0.05	0.05	0.05	0.35	0.35	0.35	0.35	0.35	0.35	0.35

Amounts shown are percentages.

EXAMPLE 3

STABLE UNIT DOSE FORMULATIONS

[00163] Formulations of calcitriol were prepared to yield the compositions in Table 3. The Vitamin E TPGS was warmed to approximately 50°C and mixed in the appropriate ratio with MIGLYOL 812. BHA and BHT were added to each formulation to achieve 0.35% w/w of each in the final preparations.

TABLE 3: Calcitriol formulations

Formulation #	MIGLYOL (% wt/wt)	Vitamin E TPGS (% wt/wt)
1	100	0
2	95	5
3	90	10
4	50	50

[00164] After formulation preparation, Formulations 2-4 were heated to approximately 50°C and mixed with calcitriol to produce 0.1 μg calcitriol/mg total formulation. The formulations contained calcitriol were then added (~250 μL) to a 25 mL volumetric flask and deionized water was added to the 25 mL mark. The solutions were then vortexed and the absorbance of each formulation was measured at 400 nm immediately after mixing (initial) and up to 10 min after mixing. As shown in Table 4, all three formulations produced an opalescent solution upon mixing with water. Formulation 4 appeared to form a stable suspension with no observable change in absorbance at 400 nm after 10 min.

TABLE 4: Absorption of formulations suspended in water

Formulation #	Absorbance at 400 nm	
	Initial	10 min
2	0.7705	0.6010
3	1.2312	1.1560
4	3.1265	3.1265

[00165] To further assess the formulations of calcitriol, a solubility study was conducted to evaluate the amount of calcitriol soluble in each formulation.

Calcitriol concentrations from 0.1 to 0.6 μg calcitriol/mg formulation were prepared by heating the formulations to 50°C followed by addition of the appropriate mass of calcitriol. The formulations were then allowed to cool to room temperature and the presence of undissolved calcitriol was determined by a light microscope with and without polarizing light. For each formulation, calcitriol was soluble at the highest concentration tested, 0.6 μg calcitriol/mg formulation.

[00166] Forty-five μg and 180 μg calcitriol doses are currently being used in Phase 2 human clinical trials. To develop a capsule with a 45 μg dosage, each formulation was prepared with 0.2 μg calcitriol/mg formulation and 0.35% w/w of both BHA and BHT. The bulk formulation mixtures were filled into Size 3 hard gelatin capsules at a mass of 225 mg (45 μg calcitriol). The capsules were then analyzed for stability at 5°C, 25°C/60% relative humidity (RH), 30°C/65% RH, and 40°C/75% RH. At the appropriate time points, the stability samples were analyzed for content of intact calcitriol and dissolution of the capsules. The calcitriol content of the capsules was determined by dissolving three opened capsules in 5 mL of methanol and held at 5°C prior to analysis. The dissolved samples were then analyzed by reversed phase HPLC. A Phemonex Hypersil BDS C18 column at 30°C was used with a gradient of acetonitrile from 55% acetonitrile in water to 95% acetonitrile at a flow rate of 1.0 mL/min during elution. Peaks were detected at 265 nm and a 25 μL sample was injected for each run. The peak area of the sample was compared to a reference standard to calculate the calcitriol content as reported in Table 5. The dissolution test was performed by placing one capsule in each of six low volume dissolution containers with 50 mL of deionized water containing 0.5% sodium dodecyl sulfate. Samples were taken at 30, 60 and 90 min after mixing at 75 rpm and 37 °C. Calcitriol content of the samples was determined by injection of 100 μL samples onto a Betasil C18 column operated at 1 mL/min with a mobile phase of 50:40:10 acetonitrile:water:tetrahydrofuran at 30°C (peak detection at 265 nm). The mean value from the 90 min dissolution test results of the six capsules was reported (Table 6).

[00167] The chemical stability results indicated that decreasing the MIGLYOL 812 content with a concomitant increase in Vitamin E TPGS content provided enhanced recovery of intact calcitriol as noted in Table 5. Formulation 4 (50:50 MIGLYOL 812/Vitamin E TPGS) was the most chemically stable formulation with only minor decreases in recovery of intact calcitriol after 3 months at 25°C/60% RH, enabling room temperature storage.

TABLE 5: Chemical stability of calcitriol formulation in hard gelatin capsules (225 mg total mass filled per capsule, 45 μg calcitriol)

Storage Condition	Time (mos)	Assay[a] (%) Form. 1	Form. 2	Form 3	Form 4
N/A	0	100.1	98.8	99.1	100.3
5°C	1.0	99.4	98.9	98.9	104.3
25°C/60% RH	0.5	99.4	97.7	97.8	102.3
	1.0	97.1	95.8	97.8	100.3
	3.0	95.2	93.6	96.8	97.9
30°C/65% RH	0.5	98.7	97.7	96.8	100.7
	1.0	95.8	96.3	97.3	100.4
	3.0	94.2	93.6	95.5	93.4
40°C/75% RH	0.5	96.4	96.7	98.2	97.1
	1.0	96.1	98.6	98.5	99.3
	3.0	92.3	92.4	93.0	96.4

a. Assay results indicate % of calcitriol relative to expected value based upon 45 μg content per capsule. Values include pre-calcitriol which is an active isomer of calcitriol.

TABLE 6: Physical Stability of Calcitriol Formulation in Hard Gelatin Capsules (225 mg total mass filled per capsule, 45 μg calcitriol)

Storage Condition	Time (mos)	Dissolution[a] (%) Form. 1	Form. 2	Form 3	Form 4
N/A	0	70.5	93.9	92.1	100.1
5°C	1.0	71.0	92.3	96.0	100.4
25°C/60% RH	0.5	65.0	89.0	90.1	98.3
	1.0	66.1	90.8	94.5	96.2
	3.0	64.3	85.5	90.0	91.4
30°C/65% RH	0.5	62.1	88.8	91.5	97.9
	1.0	65.1	89.4	95.5	98.1
	3.0	57.7	86.4	89.5	88.8
40°C/75% RH	0.5	91.9	90.2	92.9	93.1
	1.0	63.4	93.8	94.5	95.2
	3.0	59.3	83.6	87.4	91.1

a. Dissolution of capsules was performed as described and the % calcitriol is calculated based upon a standard and the expected content of 45 μg calcitriol

per capsule. The active isomer, pre-calcitriol, is not included in the calculation of % calcitriol dissolved. Values reported are from the 90 min sample.

[00168] The physical stability of the formulations was assessed by the dissolution behavior of the capsules after storage at each stability condition. As with the chemical stability, decreasing the MIGLYOL 812 content and increasing the Vitamin E TPGS content improved the dissolution properties of the formulation (Table 6). Formulation 4 (50:50 MIGLYOL 812/Vitamin E TPGS) had the best dissolution properties with suitable stability for room temperature storage.

EXAMPLE 4

PHASE II CLINICAL TRIAL

[00169] Two hundred fifty patients with androgen independent prostate cancer were enrolled in a randomized placebo controlled trial at 48 centers in the United States and Canada. All patients in the study received chemotherapy treatment with weekly Taxotere®, a drug in the taxoid class of chemotherapeutic agents. Taxotere® is approved for use in prostate cancer and some other types of cancer. Oral dexamethasone was also given along with the Taxotere® to minimize certain side effects (allergic reactions and fluid retention) associated with Taxotere®.

[00170] In addition to Taxotere® and dexamethasone, half of the patients were randomly treated with calcitriol and the other half received a placebo. Calcitriol was administered as three capsules of 15 μg each once a week on the day prior to chemotherapy. Previous studies in more than 90 cancer patients suggested that weekly dosing allows patients to receive high doses of calcitriol while minimizing the side effect of high blood calcium (hypercalcemia). The same Taxotere® dose of 36 mg/m^2 body surface area was administered to the patients receiving Taxotere® and placebo or Taxotere® in combination with calcitriol. Drugs were administered for three weeks out of a four week cycle, with calcitriol being administered on days 1, 7, and 21 and Taxotere® being administered on days 2, 8, and 22.

[00171] Patients receiving Taxotere® and calcitriol by HDPA experienced fewer pulmonary disorders compared to patients treated with Taxotere® without calcitriol. These disorders include pneumonia where five of 125 patients treated with Taxotere® alone developed a serious adverse event classified as pneumonia as compared to four on Taxotere® and calcitriol. One patient on Taxotere® developed ARDS and four were hospitalized for dyspnea while none of the patients receiving Taxotere® and calcitriol developed ARDS or were hospitalized for dyspnea. In those serious adverse pulmonary events judged by the blinded investigators to be probably related to Taxotere®, five occurred on Taxotere® alone while one occurred on Taxotere® and calcitriol.

[00172] Having now fully described the invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A method for preventing, treating or ameliorating a pulmonary disorder in a patient receiving one or more chemotherapeutic or radiotherapeutic agents or treatments, said method comprising administering to the patient a pharmaceutical composition comprising an effective amount of active vitamin D compound or a mimic thereof.

2. The method of claim 1, wherein said active vitamin D compound or a mimic thereof is administered by high dose pulse administration (HDPA), wherein each pulsed dose is a sufficient amount to have a therapeutic effect.

3. The method of claim 1, wherein said active vitamin D compound is calcitriol.

4. The method of claim 2, wherein said active vitamin D compound is administered as a unit dosage form comprising about 10 μg to about 5 mg of calcitriol, about 50% MIGLYOL 812 and about 50% tocopherol PEG-1000 succinate (vitamin E TPGS).

5. The method of claim 2, wherein said active vitamin D compound is administered as a unit dosage form comprising about 45 μg of calcitriol, about 50% MIGLYOL 812, about 50% vitamin E TPGS, BHA, and BHT.

6. The method of claim 5, wherein said unit dosage form comprises about 50% MIGLYOL 812, about 50% vitamin E TPGS, about 0.05% to about 0.35% BHA, and about 0.05% to about 0.35% BHT.

7. The method of claim 6, wherein said unit dosage form comprises about 50% MIGLYOL 812, about 50% vitamin E TPGS, about 0.35% BHA, and about 0.10% BHT.

8. The method of claim 4, wherein said unit dosage form is a capsule wherein the total volume of ingredients in said capsule is between about 10 μL to about 1000 μL.

9. The method of claim 2, wherein said HDPA is administered no more frequently than once in three days.

10. The method of claim 1, wherein said patient is suffering from one or more cancers selected from the group consisting of brain cancer, breast cancer, gastrointestinal cancers comprising colon, colorectal, esophageal, gastric, hepatocellular, pancreatic and rectal cancers, genitourinary cancers comprising bladder, prostate, renal cell and testicular cancers, gynecologic cancers comprising cervical, endometrial, ovarian and uterine cancers, head and neck cancer, leukemias comprising acute lymphoblastic, acute myelogenous, acute promyelocytic, chronic lymphocytic, chronic myelogenous and hairy cell leukemias, non-small-cell and small-cell lung cancers, Hodgkin's and non-Hodgkin's lymphomas, melanoma, multiple myeloma and sarcoma.

11. The method of claim 1, wherein said one or more chemotherapeutic agents are selected from the group consisting of actinomycin D, irinotecan, vincristine, vinblastine, methotrexate, azathioprine, fluorouracil, doxorubicin, mitomycin, docetaxel, paclitaxel, cyclophosphamide, capecitabine, epirubicin, cisplatin, gemcitabine, mitoxantrone, leucovorin, vinorelbine, SN-38, azacitidine, thalidomide, trastuzumab, etoposode, carboplatin, estramustine, prednisone, interferon alpha-2a, interleukin-2, bleomycin, ifosfamide, mesna, altretamine, topotecan, cytarabine, methylprednisolone, dexamethasone, daunorubicin, intrathecal

methotrexate, mercaptopurine, thioguanine, fludarabine, gemtuzumab, idarubicin, mitoxantrone, tretinoin, alemtuzumab, chlorambucil, cladribine, interferon α_{2b}, hydroxyurea, imatinib, epirubicin, dacarbazine, procarbazine, mechlorethamine, rituximab, denileukin diftitox, trimethoprim/sulfamethoxazole, allopurinol, carmustine, tamoxifen, filgrastim, temozolomide, melphalan, thalidomide and mitomycin.

12. The method of claim 1, wherein said one or more radiotherapeutic agent or treatment is an agent or treatment administered in external-beam radiation therapy, brachytherapy, thermotherapy, radiosurgery, charged-particle radiotherapy, neutron radiotherapy, photodynamic therapy, or radionuclide therapy.

13. The method of claim 11, wherein said one or more chemotherapeutic agents is a taxane.

14. The method of claim 13, wherein said taxane is paclitaxel, docetaxel or abraxane.

15. The method of claim 11 or 12, wherein said pulmonary disorders are induced by or associated with chemotherapy or radiotherapy.

16. The method of claim 11, wherein said pulmonary disorder is pulmonary fibrosis, acute respiratory distress syndrome, pneumonia, hypoxia or dyspnea.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/15281

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61K 31/59**(2006.01);**C07C 401/00**(2006.01)

USPC: 514/167;552/653
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/167; 552/653

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPATFULL, STN, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
x	US 6,689,766 B2 (TAKENOUCHI et al.) 10 Feb 2004, see the entire document especially abstract, column 67, lines 31-48, column 146, Examples 6-1 and Table 6-1 and claims 11-13.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

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